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(54) Pyrrole derivatives

(57) Pyrrole derivatives are described. These compounds are useful as anti-inflammatory agents in the treatment of inflammation and pain. The preparation of these compounds, their pharmaceutically acceptable salts, and pharmaceutical compositions containing these compounds, is also described.

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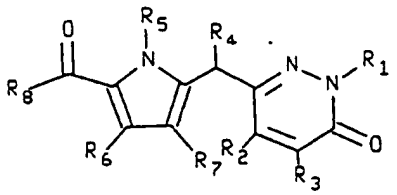
Description

Considerable effort has been devoted to the discovery of non-steroidal anti-inflammatory drugs ("NSAIDs") with reduced undesirable effects in the gastrointestinal ("GI") tract and the kidney, for exampl . Although modest improvements have been made in this area, an effective NSAID devoid of adverse GI and renal side effects has remained elusive. Related Art is known in fr m of the following referenc s.

Carson, *et al.*, U.S. Patent No.3,752,826 describes a family of aroyl-substituted pyrroles that are useful as anti-inflammatory agents. Ellis, *et al.*, U.S. Patent No. 4,766,121 pertains to a family of pyridyl and pyridazinyl substituted thyronine compounds that exhibit thyromimetic activity. Dowell, *et al.*, EP Application No. 91310784.3 describes a class of 5-lipoxygenase inhibitors that are useful as anti-inflammatory agents.

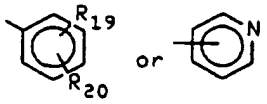
One aspect of the present invention relates to a family of compounds of Formula (Ia) having the following structure:



(Ia)

wherein:

R_1 is -H, lower alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyloxy, substituted acyloxy, lower dialkylamino, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkene, lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

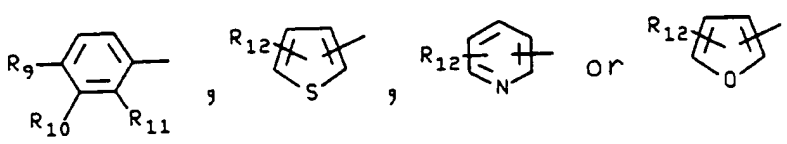
R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio; and

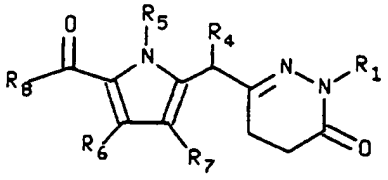
R_8 is:



where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alken r lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; and the pharmaceutically acceptable salts thereof.

More specifically the present invention is directed to such compounds of formula Ia as described above wherein R_1, R_2, R_3, R_4 is -H; R_6 is -H or lower alkyl; R_7 is -H; R_8 is a benzene ring with R_9 -H or halo and R_{10}, R_{11} is -H or R_8 is 2-thienyl with R_{12} is -H or even more specifically wherein R_5 is $-CH_3$, preferably wherein R_6 is $-CH_3$ and R_8 is a b nzene ring with R_9 is -H or halo and R_{10}, R_{11} is -H or R_8 is 2-thienyl with R_{12} is -H and more preferably wherein R_9 is -Cl or -Br.

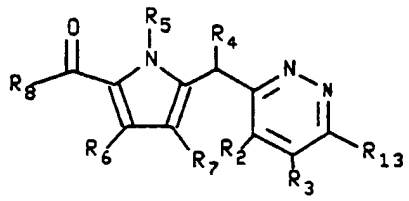
Yet another aspect of the present invention relates to a family of compounds of Formula (Ib) having the following structure:



(Ib')

wherein R_1 and R_4 to R_8 are as defined above; and the pharmaceutically acceptable salts thereof.

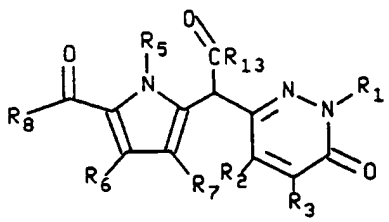
Another aspect of the present invention relates to a family of compounds of Formula (II) having the following structure:



(II)

wherein: R_2 to R_8 are as defined above and R_{13} is lower alkoxy, mercapto, lower alkylthio, $-NR_{21}R_{22}$ or $-O-(CH_2)_m-NR_{21}R_{22}$; where m is an integer from 1 to 6, R_{21} is -H or lower alkyl and R_{22} is -H or lower alkyl, and where R_{21} and R_{22} may be taken together with N to form a ring of three to five carbon atoms which may include one member that is -O-, -S-, or $-N(R_{23})-$ where R_{23} is -H or lower alkyl; and the pharmaceutically acceptable salts thereof.

Yet another aspect of the present invention relates to a family of compounds of Formula (III) having the following structure:



(III)

wherein: R_1, R_5 to R_8, and R_{13} are as defined above; and the pharmaceutically acceptable salts thereof.

In another aspect, the inv ntion relates to pharmaceutical compositi ns containing a therapeutically effective amount of a compound of Formula (Ia), (Ib), (II) or (III) or a pharmaceutically acceptable salt thereof, mixed with at least one pharmaceutically acceptable excipient.

In still another aspect, the invention relates to a method of use of compounds of Formula (Ia), (Ib), (II) and (III) as anti-inflammatory agents to treat inflammation and pain by administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (Ia), (Ib), (II) or (III) or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides compositions useful and their use in the treatment of the conditions described herein comprising a therapeutically effective amount of a compound of Formula (Ia), (Ib), (II) or (III) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Another aspect of the invention pertains to a method of selecting an NSAID that will not exhibit adverse gastrointestinal ("GI") and renal side effects, comprising the step of testing the NSAID for its ability to inhibit the enzyme activity of prostaglandin G/H synthase I (cyclooxygenase I or "COX I") and prostaglandin G/H synthase II (cyclooxygenase II or "COX II"), wherein selective inhibition of COX II over COX I is indicative of a GI and renal sparing drug.

Yet another aspect of the invention relates to the treatment of the above conditions or diseases by the selective inhibition of COX II. In particular, the invention relates to a method of treating pain and inflammation without obtaining adverse GI and renal side effects, comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the present invention especially one that selectively inhibits cyclooxygenase II over cyclooxygenase I.

Before proceeding further with the description of the specific embodiments of the present invention, a number of terms will be defined.

The term "alkyl" refers to a monovalent radical containing only carbon and hydrogen, and which may be a fully saturated branched or straight chain radical, or a ring of carbon atoms linked together by single bonds. This term is further exemplified by radicals such as methyl ($-CH_3$), ethyl, t-butyl, pentyl, pivalyl, heptyl, cyclo-propyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl-methyl, adamantyl, and the like.

The term "lower alkyl" refers to a cyclic, branched or straight chain monovalent alkyl radical of one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), cyclopropylmethyl, i-amyl, n-amyl and hexyl.

The term "hydroxy" refers to the radical, -OH. The term "lower alkoxy" refers to the group -O-R where R is a lower alkyl.

The term "acetyl" refers to the radical $-C(O)CH_3$. The term "substituted acetyl" refers to an acetyl where 1-3 of the hydrogens have been replaced by a radical selected from the group consisting of lower alkyl, acetoxy ($-O-C(O)-CH_3$) and amino.

The term "lower acyloxy" refers to the radical, -O-C(O)-R, where R is a lower alkyl. The term "substituted acyloxy" refers to an acyloxy where 1-3 of the hydrogens have been replaced by a radical selected from the group consisting of lower alkyl, acetoxy and amino.

The term "lower alkylthio" refers to the group -S-R, where R is a lower alkyl. This term is exemplified by such radicals as methylthio, $-SCH_3$.

The term "lower alkylsulfinyl" refers to the group -S(O)-R, where R is a lower alkyl. This term is exemplified by such radicals as methylsulfinyl, $-S(O)CH_3$.

The term "lower alkylsulfonyl" refers to the group $-S(O)_2-R$, where R is a lower alkyl. This term is exemplified by such radicals as methylsulfonyl, $-S(O)_2CH_3$.

The term "lower alkene" refers to an unsaturated branched or straight chain alkene radical of two to six carbon atoms and containing a double bond. This term is further exemplified by such radicals as ethylene and propylene.

The term "lower alkyne" refers to an unsaturated branched or straight chain alkyne radical of two to six carbon atoms and containing a triple bond. This term is further exemplified by such radicals as acetylene, propyne and butyne.

The term "cyano" refers to the radical, -CN.

The term "halo" refers to fluoro, bromo, chloro and iodo.

The term "halo-lower alkyl" refers to a lower alkyl substituted with one to three halo groups, and is further exemplified by such radicals as $-CF_3$, $-CH_2CF_3$ and $-CH_2CCl_3$.

The term "amino" refers to the radical $-NH_2$. The term "lower dialkylamino" refers to two lower alkyl groups bound to an amino group, and is further exemplified by such radicals as dimethylamino, $-N(CH_3)_2$.

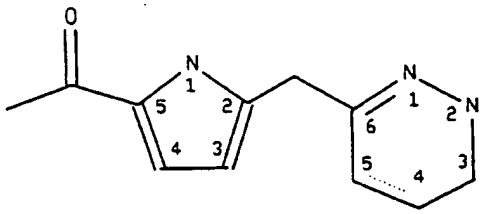
The term "mercapto" refers to the radical, -SH.

The term "methane sulfonamido" refers to the radical, $-NHS(O)_2CH_3$.

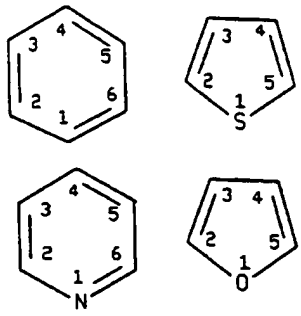
The term "pharmaceutically acceptable salt" is a salt of a compound of the invention that retains the biological effectiveness and properties of the compound of the invention and which is not biologically or otherwise undesirable. Salts may be derived from inorganic or organic acids and bases, and include pharmaceutically acceptable anions, the anions of acid addition salts, and pharmaceutically acceptable cations, the cations of base addition salts. Acid addition salts are derived from inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate salts), nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, xalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, salicylic acid, *p*-toluenesulfonic acid, and the like. Base addition salts may be derived from inorganic bases such as sodium hydroxide, potassium hydrox-

ide, lithium hydroxide, ammonium, calcium hydroxide, magnesium hydroxide, and the like. Salts derived from organic bases include those formed from primary, secondary and tertiary amin s, substituted amines including naturally occurring substituted amines, and cyclic amines, including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, pyridine, cyclohexylamine, ethylene diamine, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylene-diamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, and the like. Preferred organic bases are isopropylamine, diethyl-amine, monoethanolamine, diethanolamine, triethanolamine, piperidine, tromethamine, and choline.

The naming and numbering of the compounds of the present invention is illustrated below. The pyrrole pyridazine/pyridazinone nucleus of the compounds of Formula (Ia), (Ib), (II) and (III) is numbered as follows:



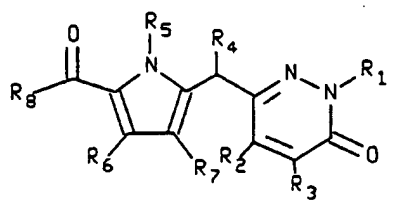
Side chains of the R_8 substituent are numbered as shown below:



The thiophene, pyridine and furan rings can be linked to the pyrrole carbonyl group at any position on the ring. Accordingly, the thiophene ring can be 2- or 3-thienyl, the pyridine ring can be 2-, 3-, or 4-pyridyl, and the furan ring can be 2- or 3-furyl.

This invention relates to families of compounds that are non-steroidal anti-inflammatory drugs and which do not exhibit gastrointestinal ("GI") and renal side effects when administered at doses sufficient to achieve an anti-inflammatory effect.

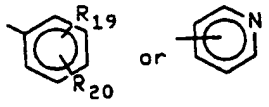
The invention relates to a family of compounds of Formula (Ia) having the following structure:



(Ia)

wherein:

R_1 is -H, lower alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyloxy, substituted acyloxy, lower dialkylamino, lower alkylsulfanyl, lower alkylsulfinyl, lower alkylsulfonyl, lower alkene, lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

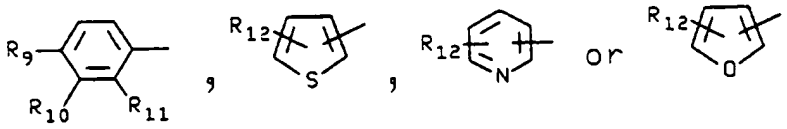
R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylsulfanyl; and

R_8 is:



where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylsulfanyl, lower alkoxy, lower alkene or lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; and the pharmaceutically acceptable salts thereof.

Representative compounds of Formula (Ia), where $R_1=R_2=R_3=R_4=H$, $R_5=CH_3$, $R_7=H$, and R_8 is a benzene ring, are as follows:

#	R_6	R_9	R_{10}	R_{11}	Melting point, °C (solvent of crystallization)
16	CH_3	Cl	H	H	202-203 (acetone:hexane)
30	CH_3	CH_3	H	H	233-235 (CH_2Cl_2:CH_3OH)
31	CH_3	OCH_3	H	H	198-200 (CH_2Cl_2:CH_3OH)
32	CH_3	H	H	H	164-166 (CH_2Cl_2:EtOAc)
33	CH_3	$CHCH_2$	H	H	190-192 (hexane:acetone)
34	CH_3	SCH_3	H	H	205-207 (CH_2Cl_2:hexane)
35	CH_3	Br	H	H	224-226 (CH_2Cl_2:acetone)
36	CH_3	CH_2CH_3	H	H	228-229 (CH_3OH:acetone)
37	H	CH_3	CH_3	H	195-197 (hexane:EtOAc)
38	H	H	CH_3	H	172-174 (hexane:acetone)
39	H	Cl	H	H	168-170 (EtOAc)
40	H	H	Cl	H	165-170 (CH_3OH)
41	H	H	H	Cl	190-192 (EtOAc)
42	H	cyclopropyl	H	H	182-183 (CH_2Cl_2:hexane)
43	H	SCH_3	H	H	190-191 (EtOAc)
44	H	$N(CH_3)_2$	H	H	178-179 (CH_2Cl_2:hexane)
45	H	$CH(CH_3)_2$	H	H	162-163 (CH_2Cl_2:hexane)
46	H	CH_2CH_3	H	H	164-166 (CH_2Cl_2:hexane)
47	H	Cl	H	Cl	179-180 (EtOAc)
48	H	F	H	H	200-201 (CH_3OH)
49	H	H	H	CH_3	170-172 (hexane:EtOAc)
50	H	SCH_2CH_3	H	H	164-165 (hexane:EtOAc)
51	H	CH_3	H	CH_3	166-167 (hexane:EtOAc)
52	H	CF_3	H	H	186-188 (hexane:EtOAc)
53	H	OCH_3	H	H	198-199 (EtOAc)

#	R_6	R_9	R_{10}	R_{11}	Melting point, °C (solvent of crystallization)
54	H	$CHCH_2$	H	H	186-188 (hexane:ac tone)
55	H	$C(CH_3)_3$	H	H	171-173 (EtOAc)
56	H	H	H	H	162-163 (hexane:acetone)
57	H	Br	H	H	186-187 (hexane:acetone)
58	H	$O(CH_2)_2CH_3$	H	H	174-176 (hexane:acetone)
59	H	$OCH(CH_3)_2$	H	H	138-140 (hexane:acetone)
60	H	OCH_2CH_3	H	H	180-182 (hexane:acetone)
65	H	C≡CH	H	H	185-187 (hexane:acetone)
100	H	CH_3	H	H	227.2-227.4 (EtOAc)
106	H	$NHCOCH_3$	H	H	252-254 (acetone:CH_3OH)
142	CH_3	F	H	H	193-194 (CH_2Cl_2:CH_3OH)
167	SCH_3		Cl	H	192-193 (CH_2Cl_2:hexane)

and are named:

16. 6-[1,4-dimethyl-5-(4-chloro-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
30. 6-[1,4-dimethyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
31. 6-[1,4-dimethyl-5-(4-methoxy-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
32. 6-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
33. 6-[1,4-dimethyl-5-(4-vinyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
34. 6-[1,4-dimethyl-5-(4-methylsulfanyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
35. 6-[5-(4-bromo-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
36. 6-[1,4-dimethyl-5-(4-ethyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
37. 6-[5-(3,4-dimethyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
38. 6-[1-methyl-5-(3-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
39. 6-[5-(4-chloro-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
40. 6-[5-(3-chloro-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
41. 6-[5-(2-chloro-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
42. 6-[5-(4-cyclopropyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
43. 6-[1-methyl-5-(4-methylsulfanyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
44. 6-[5-(4-dimethylamino-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
45. 6-[5-(4-isopropyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
46. 6-[5-(4-ethyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
47. 6-[5-(2,4-dichloro-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
48. 6-[5-(4-fluoro-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
49. 6-[1-methyl-5-(2-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
50. 6-[5-(4-ethylsulfanyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
51. 6-[5-(2,4-dimethyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
52. 6-[1-methyl-5-(4-trifluoromethyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
53. 6-[5-(4-methoxy-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
54. 6-[1-methyl-5-(4-vinyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
55. 6-[5-(4-tert-butyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
56. 6-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
57. 6-[5-(4-bromo-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
58. 6-[1-methyl-5-(4-{1-propyl}oxy-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
59. 6-[1-methyl-5-(4-{2-propyl}oxy-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
60. 6-[5-(4-ethoxy-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
65. 6-[5-(4-ethynyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
100. 6-[1-methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;

106. N-[4-[1-Methyl-5-(6-oxo-1,6-dihydro-pyridazin-3-ylmethyl)-1H-pyrrol-2-ylcarbonyl]-phenyl]-acetamide;
142. 6-[1,4-dimethyl-5-(4-fluoro-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one; and
167. 6-[5-(4-chloro-benzoyl)-1-methyl-4-methylsulfanyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one.

Representative compounds of Formula (Ia) where $R_1=R_2=R_3=R_4=H$, $R_5=CH_3$, $R_6=Cl$, $R_7=H$, R_8 is a benzene ring and $R_{10}=R_{11}=H$, are as follows:

#	R_9	Melting point,°C (solvent of crystallization)
80	CH_3	191-193 (EtOAc:hexane)
81	Cl	182-184 (EtOAc)
82	OCH_3	162-264 (CH_2Cl_2:hexane)

and are named:

80. 6-[4-chloro-1-methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
81. 6-[4-chloro-5-(4-chloro-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one; and
82. 6-[4-chloro-5-(4-methoxy-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one.

Representative compounds of Formula (Ia) where $R_1=R_2=R_3=R_7=H$, R_8 is a benzene ring and $R_{10}=R_{11}=H$, are as follows:

#	R_4	R_5	R_6	R_9	Melting point,°C (solvent of crystallization)
9	CN	CH_3	CH_3	Cl	224-227.5 (EtOAc:hexane)
18	CH_3	CH_3	CH_3	Cl	194.1-196.0 (acetone)
86	H	CH_2CH_3	H	CH_3	176-178 (EtOAc)
95	CH_3	CH_3	H	CH_3	201.8-202.3 (acetone:hexane)

and are named:

9. [5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl) acetonitrile;
18. 6-{1-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-ethyl}-2H-pyridazin-3-one;
86. 6-[1-ethyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one; and
95. 6-{1-[1-methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-yl]-ethyl}-2H-pyridazin-3-one.

Representative compounds of Formula (Ia) where $R_1=R_2=R_3=R_4=H$, $R_5=CH_3$, R_8 is a benzene ring, and $R_{10}=R_{11}=H$, are as follows:

#	R_6	R_7	R_9	Melting point,°C (solvent of crystallization)
24	CH_3	Cl	Cl	247.2-248.5 (EtOAc)
25	CH_3	Br	Cl	231.0-231.5 (EtOAc)
87	H	Cl	CH_3	212-214 (EtOAc)
88	H	Cl	OCH_3	193-195 (EtOAc)
89	CH_3	Cl	H	250-251 (CH_2Cl_2:acetone)
107	SCH_3	H	CH_3	182-184 (EtOAc)
130	H	Br	CH_3	220-221 (CH_2Cl_2:EtOAc)

and are named:

24. 6-[3-chloro-5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
25. 6-[3-bromo-5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
87. 6-[3-chloro-1-methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
88. 6-[3-chloro-5-(4-methoxy-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
89. 6-(5-Benzoyl-3-chloro-1,4-dimethyl-1H-pyrrol-2-ylmethyl)-2H-pyridazin-3-one;
107. 6-(1-methyl-5-(4-methyl-benzoyl)-4-methylsulfanyl-1H-pyrrol-2-ylmethyl)-2H-pyridazin-3-one; and
130. 6-[3-bromo-1-methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one.

Representative compounds of Formula (Ia) where R_1=H, R_3=CH_3, R_4=H, R_5=R_6=CH_3 and R_7=H, R_8 is a benzene ring, R_9=Cl and R_{10}=R_{11}=H, are as follows:

#	R_2	Melting point, °C (solvent of crystallization)
141	H	219-222 (EtOAc)
164	CH_3	261-261.5 (EtOAc:hexane)

and are named:

141. 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-4-methyl-2H-pyridazin-3-one; and
164. 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-4,5-dimethyl-2H-pyridazin-3-one.

Representative compounds of Formula (Ia) where R_1=R_2=R_3=R_4=H, R_5=CH_3 and R_7=H, are as follows:

#	R_6	R_8	R_{12}	Melting point,°C (solvent of crystallization)
62	H	2-thienyl	H	200-202 (CH_2Cl_2:hexane)
63	H	2-thienyl	CH_3	192-193 (EtOAc:hexane)
98	H	4-pyridyl	H	202-203 (CH_3OH:EtOAc)
99	H	3-pyridyl	H	170-172 (THF:EtOAc)
110	H	2-furyl	H	198-200 (hexane:EtOAc)
113	H	3-furyl	H	190-191 (CH_3OH:EtOAc)
144	CH_3	2-thienyl	H	188-189 (CH_2Cl_2:hexane)

and are named:

62. 6-[1-methyl-5-(thiophen-2-yl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
63. 6-[1-methyl-5-(5-methyl-thiophen-2-yl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
98. 6-[1-methyl-5-(pyridin-4-ylcarbonyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
99. 6-[1-methyl-5-(pyridin-3-ylcarbonyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
110. 6-[5-(furan-2-ylcarbonyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
113. 6-[5-(furan-3-ylcarbonyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one; and
144. 6-[1,4-dimethyl-5-(thiophen-2-ylcarbonyl)-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one.

Representative compounds of Formula (Ia) where R_2=R_3=R_4=H, R_5=R_6=CH_3, R_7=H, R_8 is a benzene ring, R_9=Cl, R_{10}=R_{11}=H, and R_1 is lower alkyl, halo-lower alkyl, acetyl or substituted acetyl, are as follows:

#	R_1	Melting point, °C (solvent of crystallization)
23	CH_3	139.9-140.2 (acetone:hexane)
114	$C(O)CH_3$	150.5-153.3 (EtOAc)
123	$(CH_2)_2F$	137.5-138.0 (hexane:EtOAc)
131	$(CH_2)_2Cl$	134.3-135 (EtOAc:hexane)
165	$C(O)C(CH_3)_2OC(O)CH_3$	103-106 (hexane:EtOAc)

and are named:

23. 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2-methyl-2H-pyridazin-3-one;
114. 2-acetyl-6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
123. 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2-(2-fluoro-ethyl)-2H-pyridazin-3-one;
131. 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2-(2-chloro-ethyl)-2H-pyridazin-3-one; and
165. acetic acid 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-1,1-dimethyl-2-oxo-ethyl ester.

Representative compounds of Formula (Ia) where R_2=R_3=R_4=H, R_5=R_6=CH_3, R_7=H, R_8 is a benzene ring, R_9=Cl, R_{10}=R_{11}=H, and R_1 is $-(CHR_{24})(CH_2)_nR_{14}$, are as follows:

#	R_1	Melting point, °C (solvent of crystallization)
118	$(CH_2)_2OH$	151-152.2 (EtOAc:hexane)
122	CH_2CN	172.2-172.7 (hexane:EtOAc)
124	$(CH_2)_2OCH_3$	113.3-114.2 (hexane:EtOAc)
126	$(CH_2)CCH$	167-168 (EtOAc:hexane)
127	$(CH_2)CHCH_2$	103-104.6 (hexane:EtOAc)
135	$(CH_2)_2OC(O)CH_3$	94.7-96 (hexane:EtOAc)
136	$(CH_2)_2NHS(O)_2CH_3$	148-149 (hexane:EtOAc)
140	$(CH_2)_3OH$	126-128.3 (EtOAc:$(C_2H_5)_2O$)
145	$(CH_2)_2CN$	135.2-136.3 (hexane:EtOAc)
149	$CH_2OC(O)C(CH_3)_3$	113.4-114.8 (hexane:EtOAc)
153	CH_2OH	176-179 (CH_3OH)
161	$CH_2OC(O)CH_3$	126.8-127.4 (hexane:EtOAc)

and are named:

118. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(2-hydroxy-ethyl)-2H-pyridazin-3-one;
122. [3-[5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]6-oxo-6H-1-yl]-acetonitrile;
124. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(2-methoxy-ethyl)-2H-pyridazin-3-one;
126. 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2-prop-2-ynyl-2H-pyridazin-3-one;
127. 2-allyl-6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
135. acetic acid 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}ethyl ester;
136. N-(2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-ethyl)-methanesulfonamide;
140. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(3-hydroxy-1-propyl)-2H-pyridazin-3-one;
145. [3-[5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-2-yl]-acetontrile;
149. 2,2-Dimethyl-propionic acid-2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-methyl ester;
153. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(hydroxy-methyl)-2H-pyridazin-3-one; and
161. acetic acid 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-methyl ester.

A representative compound of Formula (Ia) where R_2=R_3=R_4=H, R_5=R_6=CH_3, R_7=H, R_8 is a benzene ring, R_9=Cl, R_{10}=R_{11}=H, and R_1 is $-(CHR_{24})(CH_2)_nC(O)R_{15}$, is as follows:

#	R_1	Melting point, °C (solvent of crystallization)
116	$(CH_2)C(O)OCH_3$	130.4-130.9 (EtOAc:hexane)

and is named:

116. {3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-acetic acid methyl ester.

Representative compounds of Formula (Ia) where R_2=R_3=R_4=H, R_5=R_6=CH_3, R_7=H, R_8 is a benzene ring, R_9=Cl, R_{10}=R_{11}=H, and R_1 is $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$, are as follows:

#	R_1	Melting point, °C (solvent of crystallization)
119	$CH_2C(O)N(CH_3)_2$	183.7-185.2 (CH_3OH)
120	$CH_2C(O)NH_2$	204-204.5 (CH_3OH)
125	$CH_2C(O)NH(CH_3)$	233.8-235.6 (CH_3OH)
128	$CH_2C(O)NH(CH_2)_3(CH_3)$	192-194 (CH_3OH)
132	$CH_2C(O)N(CH_2CH_3)_2$	153-154.5 ($(C_2H_5)_2O$:THF)
157	$CH_2C(O)NHCH(CH_3)CH_2CH_3$	199-199.8 (hexane:EtOAc)
158	$CH_2C(O)NHCH(CH_3)CH_2CH_3$ chiral of Compound (157)	198-198.8 (hexane:EtOAc)

and are named:

119. 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-N,N-dimethyl acetamide;
120. 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-acetamide;
125. 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-N-methyl acetamide;
128. 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-N-butyl-acetamide;
132. 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-N,N-diethyl-acetamide;
157. (S)-N-sec-butyl-2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-acetamide; and
158. (R)-N-sec-butyl-2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-yl}-acetamide.

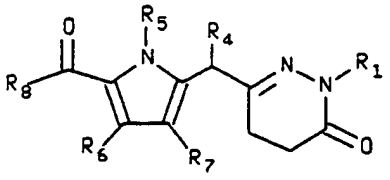
Representative compounds of Formula (Ia) where $R_2=R_3=R_4=H$, $R_5=R_6=CH_3$, $R_7=H$, R_8 is a benzene ring, $R_9=Cl$, $R_{10}=R_{11}=H$, and R_1 is $-CHR_{24}R_{18}$, are as follows:

#	R_1	Melting point, °C (solvent of crystallization)
117	3,4-dichlorobenzyl	147.9-149 (hexane:EtOAc)
121	benzyl	133.2-134.2 (hexane:EtOAc)
129	4-fluorobenzyl	162.5-163.3 (hexane:EtOAc)
133	4-chlorobenzyl	133.8-135.1 (hexane:EtOAc)
134	4-methylbenzyl	127-128 (hexane:EtOAc:ether)
137	2-fluorobenzyl	125.5-126.2 (hexane:EtOAc:ether)
138	4-cyanobenzyl	147-148.3 (hexane:CH_2Cl_2)
139	3-fluorobenzyl	141.7-142.8 (hexane:EtOAc)
146	3-cyanobenzyl	137.2-138.6 (hexane:EtOAc)
147	2-cyanobenzyl	141.1-141.9 (hexane:EtOAc)
151	2,6-dimethylbenzyl	57.0-60.5 (hexane:EtOAc)
152	2,6-dichlorobenzyl	59.0-62.5 (hexane:EtOAc)
156	3-pyridyl	156.5-157.9 (EtOAc)
168	4-methoxybenzyl	134.9-136.5 (hexane:EtOAc)

and are named:

117. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(3,4-dichloro-benzyl)-2H-pyridazin-3-one;
121. 2-benzyl-6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one;
129. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(4-fluoro-benzyl)-2H-pyridazin-3-one;
133. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(4-chloro-benzyl)-2H-pyridazin-3-one;
134. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(4-methyl-benzyl)-2H-pyridazin-3-one;
137. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(2-fluoro-benzyl)-2H-pyridazin-3-one;
138. 4-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzonitrile;
139. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(3-fluorobenzyl)-2H-pyridazin-3-one;
146. 3-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzonitrile;
147. 2-{3-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzonitrile;
151. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(2,6-dimethyl-benzyl)-2H-pyridazin-3-one;
152. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(2,6-dichloro-benzyl)-2H-pyridazin-3-one;
156. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-pyridin-3-yl-2H-pyridazin-3-one; and
168. 6-[5-(4-chloro-benzoyl)-1,4,-dimethyl-1H-pyrrol-2-ylmethyl]-2-(4-methoxy-benzyl)-2H-pyridazin-3-one.

The invention also relates to a family of compounds of Formula (Ib) having the structure:



(I b)

wherein R_1 and R_4 to R_8 are as defined above; and the pharmaceutically acceptable salts thereof.

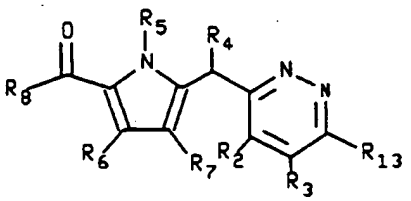
Representative compounds of Formula (Ib), where $R_1=R_4=R_7=R_{10}=R_{11}=H$ and R_8 is a benzene ring, are as follows:

#	R_5	R_6	R_9	Melting point, °C (solvent of crystallization)
94	CH_3	CH_3	Cl	198-201 (isopropanol)
102	CH_3	H	CH_3	171-172 (CH_2Cl_2:CH_3OH)

and are named:

94. 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-4,5-dihydro-2H-pyridazin-3-one; and
102. 6-[1-methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-ylmethyl]-4,5-dihydro-2H-pyridazin-3-one.

The invention also relates to a family of compounds of Formula (II) having the structure:



(I I)

wherein: R_2 to R_8 are as defined above and R_{13} is lower alkoxy, sulfanyl, lower alkylsulfanyl, $-NR_{21}R_{22}$ or $-O-(CH_2)_m-NR_{21}R_{22}$; where m is an integer from 1 to 6, R_{21} is -H or lower alkyl and R_{22} is -H or lower alkyl, and where R_{21} and R_{22} may be taken together with N to form a ring of three to five carbon atoms which may include one member that is -O-, -S-, or $-N(R_{23})-$where R_{23} is -H or lower alkyl; and the pharmaceutically acceptable salts thereof.

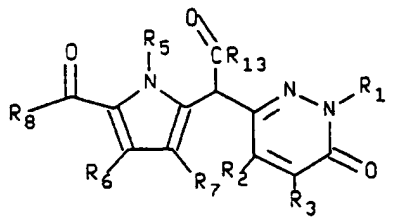
Representative compounds of Formula (II), where $R_2=R_3=R_4=H$, $R_5=R_6=CH_3$, $R_7=H$, R_8 is a benzene ring, $R_9=Cl$ and $R_{10}=R_{11}=H$, are as follows:

#	R_{13}	Melting point, °C (solvent of crystallization)
19	OCH_3	152.5-153.5 (hexane:EtOAc)
20	$OCH(CH_3)_2$	124.9-126.3 (hexane:EtOAc)
21	OCH_2CH_3	132.8-133.7 (hexane:EtOAc)
22	$O(CH_2)_2$-morpholino (Hcl salt)	132.8-133.5 (EtOAc)
96	$NHNH_2$	159-161 (water:DMSO)
103	NH_2	206.8-209 (CH_3CN:DMF:water)
169	SH	220.4-222.4 (acetone:hexane)

and are named:

19. (4-chloro-phenyl)-[5-(6-methoxy-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone;
20. (4-chloro-phenyl)-{5-[6-isopropoxy-pyridazin-3-ylmethyl]-1,3-dimethyl-1H-pyrrol-2-yl}-methanone;
21. (4-chloro-phenyl)-[5-(6-ethoxy-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone;
22. HCl salt of (4-chloro-phenyl)-{1,3-dimethyl-5-[6-(2-morpholin-4-yl-ethoxy)-pyridazin-3-ylmethyl]-1H-pyrrol-2-yl}-methanone;
96. (4-chloro-phenyl)-[5-(6-hydrazino-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone;
103. (4-chloro-phenyl)-[5-(6-amino-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone; and
169. (4-chloro-phenyl)-[5-(6-sulfanyl-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone.

The invention also relates to a family of compounds of Formula (III) having the structure:



(I I I)

wherein: R_1 to R_3, R_5 to R_8, and R_{13} are as defined above; and the pharmaceutically acceptable salts thereof.

Representative compounds of Formula (III), where $R_1=R_2=R_3=H$, $R_5=R_6=CH_3$, $R_7=H$, R_8 is a benzene ring, $R_9=Cl$ and $R_{10}=R_{11}=H$, are as follows:

#	R_{13}	Melting point, °C (solvent of crystallization)
27	OH	not characterized
28	ONa (Na salt of Compound (27))	189 ($CH_3OH:H_2O$)
29	$O(CH_2)_2$-morpholino (HCl salt)	162.5 (EtOAc:hexane)
112	OCH_3	216-217.5 (EtOAc:hexane)

and are named:

27. [5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl)-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid;
28. sodium salt of 6-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid;
29. HCl salt of [5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid 2-morpholin-4-yl-ethyl ester; and
112. [5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid methyl ester.

Studies conducted in animal models indicate that compounds of the invention exhibit the anti-inflammatory effects associated with NSAIDs, but do not exhibit the GI irritant effects common with such drugs. Similarly, these compounds have analgesic properties. These compounds are useful in the treatment of inflammation and pain caused by, for example, arthritis, gout and autoimmune disorders such as, by way of example and not limitation, systemic lupus erythematosus, rheumatoid arthritis and type I diabetes. these compounds are also useful in the treatment of cancer. The term "treatment" means any treatment of a disease in a mammal, including preventing the condition or disease by preventing the development of clinical symptoms of the disease; arresting the further progression of clinical symptoms; and relieving the condition or disease by causing the regression of clinical symptoms.

Most compounds of Formula (Ia) and (Ib) are themselves orally active selective inhibitors of prostaglandin G/H synthase II ("COX II"). However, some compounds of Formula (Ia) and (Ib) can be prodrugs that, when administered to a patient, become converted in the body to the therapeutically active compounds having Formula (Ia) or (Ib). In addition, Compounds of Formula (II) and Formula (III) may be prodrugs of the therapeutically active compounds of Formula (Ia) and (Ib).

The preferred compounds of Formula (Ia) have the following substituents. Preferably, R_1 is -H, $-(CHR_{24})(CH_2)_nR_{14}$ or $-CHR_{24}R_{18}$. More preferably, R_1 is -H, $-CH_2CN$ or $-CHR_{24}R_{18}$, where R_{18} is a benzene ring and R_{19} and R_{20} are independently selected from the group consisting of -CN, halo and lower alkyl, most preferably -CN, -Cl or $-CH_3$. Even more preferably, R_1 is -H. R_2, R_3 and R_4 are preferably -H. R_5 is preferably lower alkyl; more preferably, R_5 is $-CH_3$. R_6 is preferably lower alkyl; more preferably, R_6 is $-CH_3$. Preferably, R_7 is -H, halo or lower alkyl. More preferably, R_7 is -H, -Cl or $-CH_3$. Even more preferably, R_7 is -H. Preferably, R_8 is a benzene ring, where R_9 is halo, lower alkyl, lower alkoxy, lower alkylthio, or lower alkene, and R_{10} and R_{11} are -H. More preferably, R_9 is -Cl, -Br, $-SCH_3$, or $-CHCH_2$, with -Cl being the most preferred.

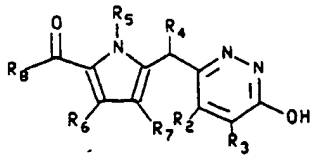
The preferred compounds of Formula (Ib) have the following substituents. Preferably, R_1 is -H, $-(CHR_{24})(CH_2)_nR_{14}$ or $-CHR_{24}R_{18}$. More preferably, R_1 is -H, $-CH_2CN$ or $-CHR_{24}R_{18}$, where R_{18} is a benzene ring and R_{19} and R_{20} are independently selected from the group consisting of -CN, halo and lower alkyl, most preferably -CN, -Cl or $-CH_3$. Even more preferably, R_1 is -H. R_4 is preferably -H. R_5 is preferably lower alkyl; more preferably, R_5 is $-CH_3$. R_6 is preferably lower alkyl; more preferably, R_6 is $-CH_3$. Preferably, R_7 is -H, halo or lower alkyl. More preferably, R_7 is -H, -Cl or $-CH_3$. Even more preferably, R_7 is -H. Preferably, R_8 is a benzene ring, where R_9 is halo, lower alkyl, lower alkoxy, lower alkylthio, or lower alkene, and R_{10} and R_{11} are -H. More preferably, R_9 is -Cl, -Br, $-SCH_3$, or $-CHCH_2$, with -Cl being the most preferred.

The preferred compounds of Formula (II) have the following substituents. R_2, R_3 and R_4 are preferably -H. R_5 is preferably lower alkyl; more preferably, R_5 is $-CH_3$. R_6 is preferably lower alkyl; more preferably, R_6 is $-CH_3$. Preferably, R_7 is -H, halo or lower alkyl. More preferably, R_7 is -H, -Cl or $-CH_3$. Even more preferably, R_7 is -H. Preferably, R_8 is a benzene ring, where R_9 is halo, lower alkyl, lower alkoxy, lower alkylthio, or lower alkene, and R_{10} and R_{11} are -H. More preferably, R_9 is -Cl, -Br, $-SCH_3$, or $-CHCH_2$, with -Cl being the most preferred. R_{13} is preferably lower alkoxy.

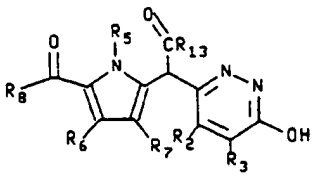
The preferred compounds of Formula (III) have the following substituents. Preferably, R_1 is -H, $-(CHR_{24})(CH_2)_nR_{14}$ or $-CHR_{24}R_{18}$. More preferably, R_1 is -H, $-CH_2CN$ or $-CHR_{24}R_{18}$, where R_{18} is a benzene ring and R_{19} and R_{20} are independently selected from the group consisting of -CN, halo and lower alkyl, most preferably -CN, -Cl or $-CH_3$. Even m re pref rably, R_1 is -H. R_2 and R_3 are preferably -H. R_5 is pr ferably lower alkyl; mor preferably, R_5 is $-CH_3$. R_6 is

preferably lower alkyl; more preferably, R_6 is $-CH_3$. Preferably, R_7 is -H, halo or lower alkyl. More preferably, R_7 is -H, -Cl or $-CH_3$. Even more preferably, R_7 is -H. Preferably, R_8 is a benzene ring, where R_9 is halo, lower alkyl, lower alkoxy, lower alkylthio, or lower alkene, and R_{10} and R_{11} are -H. More preferably, R_9 is -Cl, -Br, $-SCH_3$, or $-CHCH_2$, with -Cl being the most preferred. R_{13} is preferably lower alkoxy.

When R_1 is hydrogen, the compounds of this invention can also undergo tautomerism where compounds with an =O group on the pyridazinone ring exist in equilibrium with compounds having an -OH group. However the equilibrium lies in favor of the keto form. For example, this invention encompasses not only the compounds of Formula (Ia), but also the tautomer forms having the formula:



and the compounds of Formula (III) can exist in the tautomer form:



In addition, some compounds of Formula (II) can exist in the tautomer forms. For example, Compound (169), where R_{13} is -SH can also exist in the tautomeric thioxo form.

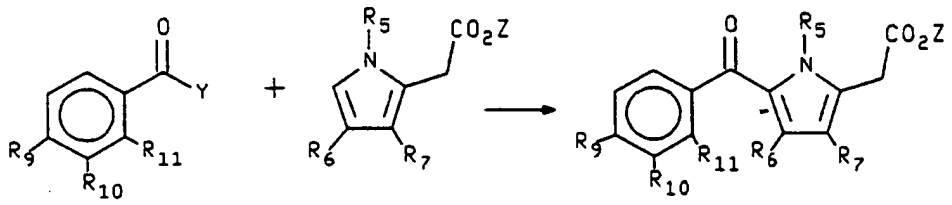
Compounds of Formula (Ia), (Ib), (II) and (III) can be made, for example, by the general reaction schemes shown below. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. or are prepared by methods known to those skilled in the art following procedures set forth in references such as, "Fieser and Fieser's Reagents for Organic Synthesis", Volumes 1-15 (John Wiley and Sons, 1991); "Rodd's Chemistry of Carbon Compounds", Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); and "Organic Reactions", Volumes 1-40 (John Wiley and Sons, 1991). These schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized and various modifications to these schemes can be made, and will be suggested to one skilled in the art.

The term "suitable solvent" means an organic solvent that is inert under the conditions of the reaction being described. Typical suitable solvents include, by way of example and not limitation, benzene, toluene, acetonitrile, tetrahydrofuran, dimethylformamide, chloroform, methylene chloride, diethyl ether, methanol, pyridine, N-methyl-pyrrolidone, ethanol, acetic acid, xylene, 1,2-dichloroethane and the like.

Scheme A is used to synthesize compounds of Formula (Ia).

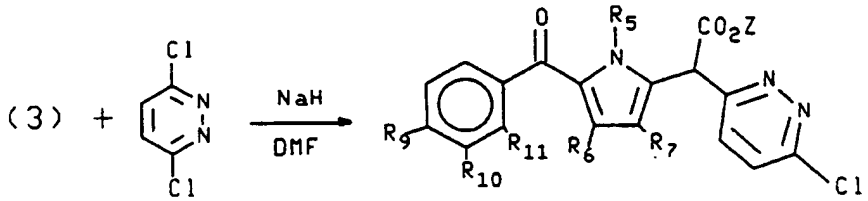
SCHEME A

Step 1



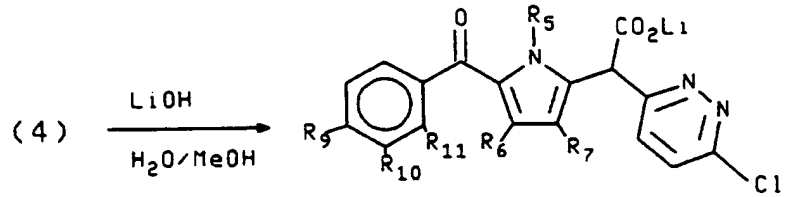
(1) Y=Cl (2) (3)

Step 2



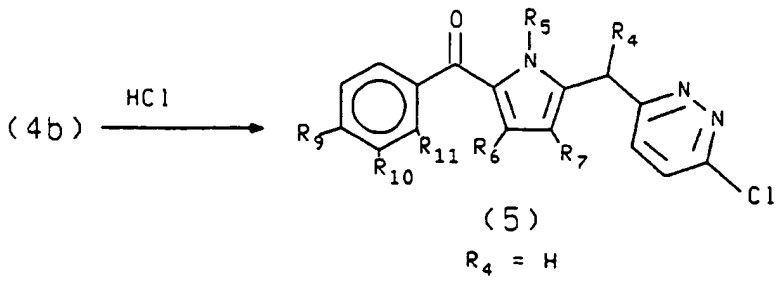
(4)

Step 3a

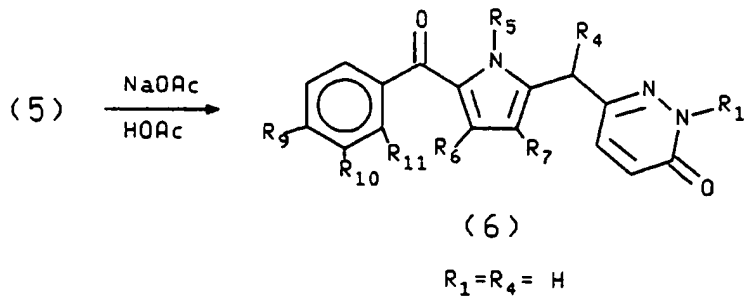


(4b)

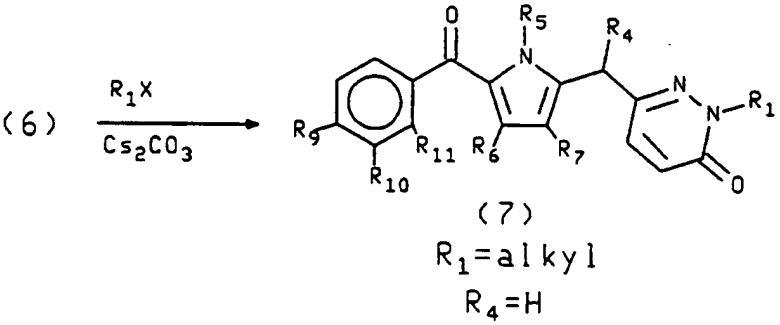
Step 3b



Step 4a



Step 4b



Step 1 is an acylation reaction of Compound (2), the pyrrole. Compound (1) is preferably a benzoyl chloride (Y=Cl) or N,N-dimethylbenzamide (Y=$N(CH_3)_2$). Preferably, Z=CH_3 or CH_2CH_3, R_5=CH_3 or CH_2CH_3, R_6=H or CH_3, R_7=H and R_{10}=R_{11}=H. When a benzoyl chloride is used, no additional reagents are needed as the reaction proceeds with only the addition of heat. When N,N-dimethylbenzamide is used, suitable reagents include, without limitation, phosphorous oxychloride, phosphorous pentachloride and oxalyl chloride. For example, using Compound (1) where Y=$N(CH_3)_2$, R_9=CH_3 and R_{10}=R_{11}=H, Compound (1) is reacted with $POCl_3$ in a suitable solvent such as dichloroethane, followed by the addition of Compound (2) in a similar solvent, where Z=CH_2CH_3 and R_5=R_6=CH_3. This is followed by the addition of sodium acetate. Alternately, Compound (1) where Y=Cl, R_9=OCH_3 and R_{10}=R_{11}=H, and Compound (2) where Z=CH_2CH_3, R_5=CH_3 and R_6=H, can be reacted in xylene.

Compound (2) can be synthesized in numerous ways. The process described by Stahley, *et al.*, J. Org. Chem. 48:4423 (1983) is useful for synthesizing Compound (2) where Z=CH_2CH_3 and R_5=R_6=CH_3.

Preferably, Compound (3) is an ester (Z=CH_3 or CH_2CH_3). However, Compound (3) may be a sodium salt (Z=Na). In the latter case, Compound (3) is treated with an alkylating reagent such as CH_3I to convert the compound to its ester form (Z=CH_3) prior to Step 2. Suitable solvents for this reaction include, for example, dimethylformamide and N-methyl

pyrrolidone. Compounds having the general formula of Compound (3) are also commercially available, for example the sodium salt of zomepirac (Compound (11) in Example 1) and tolmetin (Compound (10) in Example 17) are available from Sigma Chemical Company. Therefore, depending upon the desired Z, R_5 to R_7 and R_9 to R_{11} substituents, Step 1 can be eliminated if Compound (3), with the desired Z, R_5 to R_7 and R_9 to R_{11} substituents, is commercially available.

Step 2 is a heteroarylation reaction of Compound (3) with sodium hydride and 3,6-dichloropyridazine in an appropriate solvent, for example, dimethylformamide or N-methyl pyrrolidone.

Step 3a involves a hydrolysis reaction. Suitable hydrolysis reagents include, without limitation, lithium hydroxide, sodium hydroxide, potassium hydroxide and barium hydroxide. Step 3b is a decarboxylation reaction. Suitable decarboxylation reagents include, without limitation, hydrochloric acid, acetic acid and sulfuric acid.

Step 4a is a hydrolysis reaction and suitable hydrolysis reagents include, without limitation, sodium acetate, sodium acetate trihydrate, acetic acid, lithium hydroxide, sodium hydroxide, potassium hydroxide.

Scheme A, Steps 1 through 4a was used to synthesize numerous compounds having the structure of Formula (Ia). These include, for example, Compounds (16) and (30) through (60).

Step 4b is an alkylation reaction using R_1X, where R_1 is as defined above, and X is any leaving group, including without limitation, halo groups, methane sulfonate, p-toluene sulfonate. For example, R_1X can be a halo-alkyl, a benzyl halide, an ethyl halo acetate, and so forth. Alkylation is done in the presence of a base such as cesium carbonate, sodium hydride and potassium carbonate.

Scheme A, Steps 1 through 4b was used to synthesize Compound (23), for example.

Alternately, Step 4b is an acylation reaction using an acid chloride such as acetylchloride, and a suitable base, for example, pyridine, triethylamine, tributylamine, or N-methyl morpholine. This acylation step is used to synthesize compounds where R_1 is an acetyl or substituted acetyl, and was used to synthesize Compounds (114) and (165), for example.

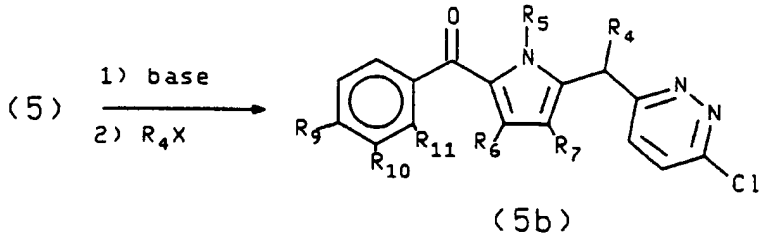
Still another alternate way of performing Step 4b involves combining Compound (6) with formaldehyde in a suitable solvent such as methanol, ethanol or isopropanol, for example. This is used to synthesize compounds where R_1 is hydroxy-methyl, and was used to synthesize Compound (153), for example.

Scheme B, below, is used to synthesize compounds of Formula (Ia) where R_4 is a lower alkyl.

SCHEME B

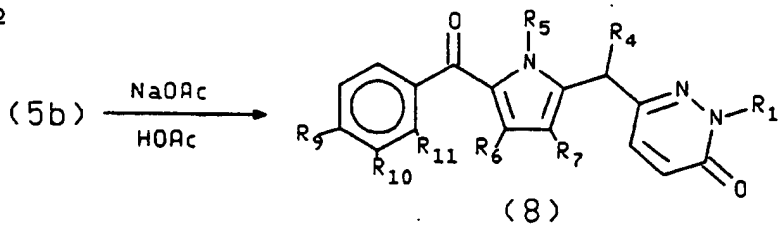
Steps 1-3 as described in Scheme A, Steps 1-3b.

Step 4a



(5b)

Step 4b



(8)

R_1=H

R_4=alkyl

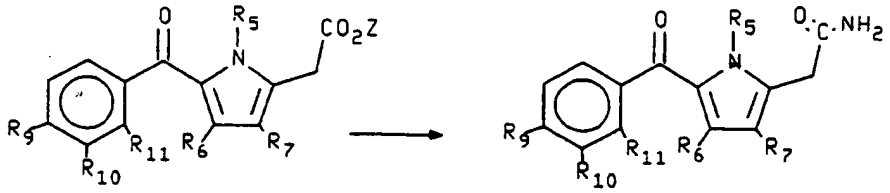
Step 4a of Scheme B involves an alkylation reaction. The alkylation reagent is R_4X, where R_4 is as defined above and X is any leaving group, as is defined above in Scheme A, Step 4b. Suitable bases for the alkylation reaction include those listed above in Scheme A, Step 4b. Step 4b of Scheme B involves hydrolysis of the chloropyridazine and suitable reagents include those listed above for Scheme A, Step 4a.

Scheme B was used to synthesize Compound (18), for example.

Scheme C, below, is used to synthesize compounds of Formula (Ia) where R_4 is cyano (-CN).

SCHEME C

Step 1

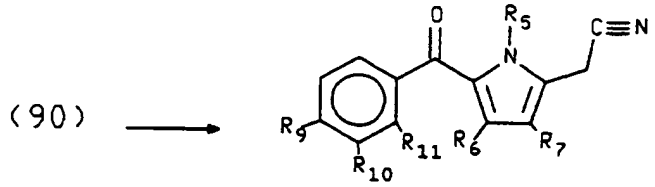


(3)

Z=H

(90)

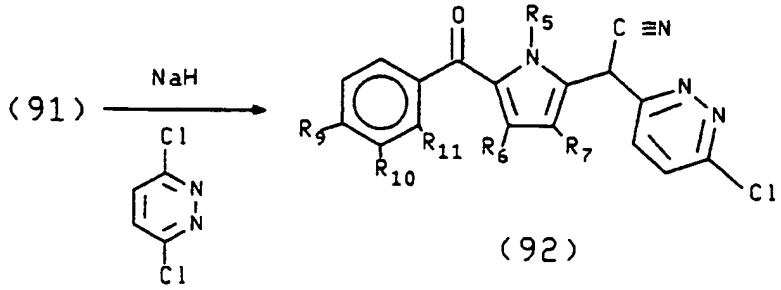
Step 2



(90)

(91)

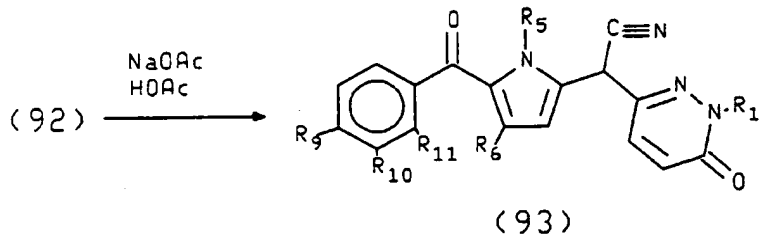
Step 3 as described in Scheme A, Step 2.



(91)

(92)

Step 4 as described in Scheme A, Step 4a.



Steps 1 and 2 involve a well established conversion of a carboxyl group to an amide. Step 1 is an amide bond formation reaction and involves reacting Compound (3) with a reagent such as ammonia.

Step 2 involves dehydration of the amide to the nitrile and involves reacting Compound (90) with a dehydrating reagent such as acetic anhydride.

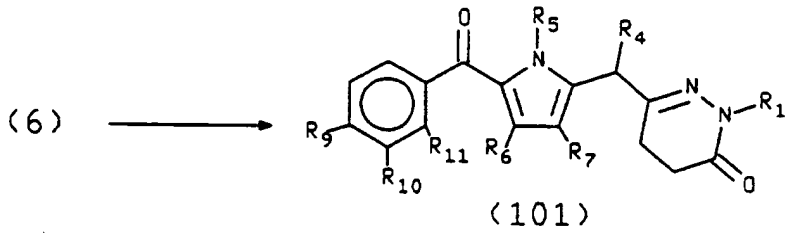
Scheme C was used to synthesize Compound (9), for example.

Scheme D, below, is used to synthesize compounds of Formula (Ib).

SCHEME D

Steps 1-4 as described for Scheme A, Steps 1-4a.

Step 5



Step 5 is a reduction step and a suitable reagent is zinc in acetic acid.

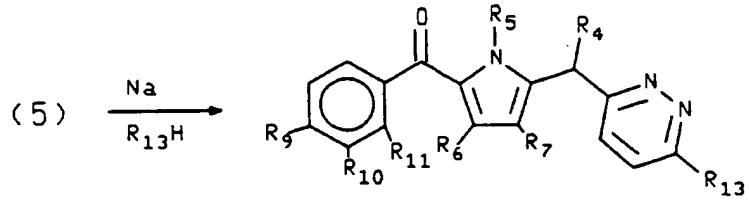
Scheme D was used to synthesize Compound (102), for example.

Scheme E, below, is used to synthesize compounds of Formula (II).

SCHEME E

Steps 1-3 as described in Scheme A, Steps 1-3b.

Step 4



(64)

Step 4 is an etherification step and $R_{13}H$ is an alcohol such as methanol, isopropanol, ethanol and morpholino ethanol. Sodium or sodium hydride can be used.

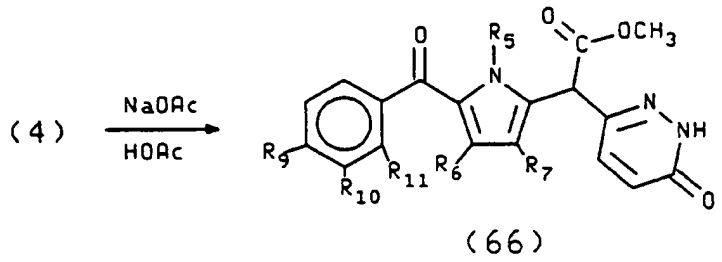
Scheme E was used to synthesize Compounds (19) through (22), for example.

Scheme F, below, is used to synthesize compounds of Formula (III):

SCHEME F

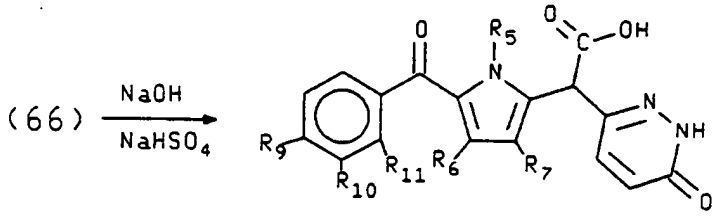
Steps 1-2: as described in Scheme A, Steps 1-2.

Step 3:



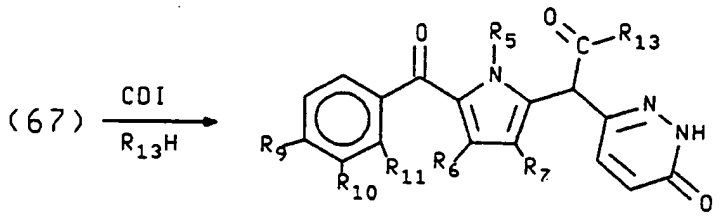
(66)

Step 4:



(67)

Step 5:



(68)

Step 3 is a hydrolysis reaction using sodium acetate in acetic acid. Step 4 is a hydrolysis reaction and suitable reagents include sodium hydroxide, lithium hydroxide and potassium hydroxide. Step 5 is an esterification reaction and $R_{13}H$ is an alcohol as described in Scheme E, Step 4. Suitable esterifying agents include, for example, carbonyldiimidazole, dicyclohexylcarbodiimide, and diisopropylcarbodiimide.

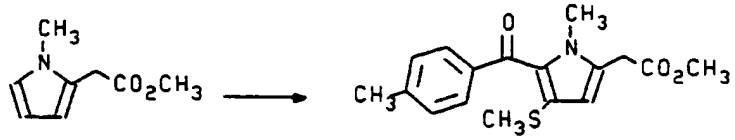
Scheme F, Steps 1-4 can be followed by a step involving the reaction of Compound (67) with a material such as sodium bicarbonate to provide the salt form of the drug, which has better water solubility. This was done to synthesize Compound (28), for example. Scheme F, Steps 1-5 was used to synthesize Compound (29), for example.

There are numerous ways to modify substituents on compounds formed by the general Schemes described above. For example, halogenation of the compounds formed in the above Schemes can also be readily accomplished. One method converts the R_7 substituent on the pyrrole from a hydrogen to a halo group. A compound such as Compound (6) is reacted with a halogenating agent in a suitable solvent to halogenate the pyrrole. Suitable halogenating agents include 1,3-dihalo-5,5-dimethyl hydantoin, N-chloro-succinimide, and N-bromosuccinimide. Suitable solvents include,

acetone, tetrahydrofuran and dimethylformamide. This method was used to synthesize Compounds (24), (25) and (87) through (89).

Compounds of the invention having the R_6 substituent as a halo group, can readily be synthesized. Compound (2) in the aforementioned Schemes can be a halogenated pyrrole where R_6 is a halo group. This halogenated pyrrole can be made by a synthesis such as that described in Example 15 for Compound (79). This method was also used to synthesize Compounds (80) through (82), for example.

Compounds of the invention having a lower alkylthio group as substituent R_6 or R_7, can also be synthesized. In any of the aforementioned Schemes, Compounds (1) and (2) can be reacted by the method described in Muchowski, *et al.*, J. Med. Chem. 32:1202 (1989):



(108) (109)

This step would then be followed by any of the subsequent steps described in the Schemes above. This method was used to synthesize the Compound (107), for example.

Compound (2) in any of the above Schemes can also be an alkylated pyrrole where R_5 is a lower alkyl group, other than methyl to provide a compound of the invention where R_5 is a lower alkyl group, other than methyl. This alkylated pyrrole can be made by a synthesis such as that done in Example 16 for Compound (85) having the following substituents: R_5=CH_2CH_3, R_6=H and Z=CH_2CH_3. This method of using an alkylated pyrrole in the above Schemes was used to synthesize Compound (86), for example.

The Schemes above illustrate the synthesis of compounds where R_8 is a benzene group. This is for illustrative purposes and is not intended to limit the Schemes in any manner, since R_8 can also be a thienyl, furyl or pyridyl group. The Schemes can be easily modified by using a thienyl-carbonyl chloride or thienyl-dimethylamide, furyl-carbonyl chloride or furyl-dimethylamide, and pyridyl-carbonyl chloride or pyridyl-dimethylamider respectively, as starting materials instead of a benzoyl chloride or N,N-dimethylbenzamide, Compound (1). For example, thienyl-carbonyl chloride was used as a starting material to synthesize Compounds (62) and (63), for example.

Compounds where R_9 is an alkyne can be readily synthesized by converting a R_9 halo group to an alkyne by a coupling reaction with an appropriate acetylene compound such as trimethylsilylacetylene and other reagents such as palladium diacetate, PPh_3 in triethylamine, and acetonitrile, followed by reaction with potassium carbonate. This is described in Example 20 for the synthesis of Compound (65).

Compounds where R_9 is a lower alkyl amido are also readily synthesized. In any one of the aforementioned Schemes, starting materials of the formula of Compound (3) can be synthesized with R_9 being a nitro group. The resulting compound is then reacted with an agent such as nickel boride followed by acetic anhydride to convert the nitro group to an amino groups, which is then converted to a lower alkyl amido group. This method was used to synthesize the starting material Compound (105) in Example 21. Compound (105) was then used to synthesize Compound (106), for example.

Isolation and purification of the above compounds and their intermediates can be done by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, preparative high pressure liquid chromatography, thin-layer chromatography, thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples set forth below. However, other equivalent separation or isolation procedures can also be used and will be suggested to one skilled in the art.

This invention also relates to pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (Ia), (Ib), (II) or (III), mixed with at least one pharmaceutically acceptable excipient.

The compounds of the present invention may exist in several crystal phases or polymorphs, which in turn, may exist in both the anhydrous and hydrate states. For example, Compound (16) has been found to exist in at least three anhydrous crystal forms and two hydrates. One skilled in the art can evaluate the factors involved to decide which phase or state is preferred for a particular pharmaceutical formulation or mode of administration. These factors include, by way of illustration and not limitation, stability, performance in chemical manufacturing, performance in biostudies (bioavailability), performance in pharmaceutical operation (blending, granulation, high speed tablet and capsule machines) and product stability (interaction with excipients).

The compounds of this invention can be incorporated into a pharmaceutical composition either in the hydrated or anhydrous form. Preferably the compound is in its hydrated form.

The term "therapeutically effective amount" refers to the amount of the compound which, when administered to a mammal in need thereof, is sufficient to effect treatment as an anti-inflammatory agent and/or analgesic agent. The amount that constitutes a "therapeutically effective amount" will vary depending on the compound, the condition or disease and its severity, and the mammal to be treated, its weight, age, etc., but may be determined routinely by one of ordinary skill in the art with regard to contemporary knowledge and to this disclosure.

This invention also relates to a method of use of compounds of Formula (Ia), (Ib), (II) and (III) as anti-inflammatory agents to treat inflammation and pain by administering to a mammal in need of such treatment a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof. This method also is useful to treat cancer.

A key aspect of this invention is that the compounds of Formula (Ia), (Ib), (II) and (III) are useful as anti-inflammatory agents but do not exhibit the adverse gastrointestinal ("GI") side effects commonly associated with NSAIDs. Similarly, it is expected that these compounds will not exhibit adverse renal side effects. This has been shown in Example 38 for Compound (16).

In another aspect, this invention provides compositions useful in the treatment of the above conditions comprising a therapeutically effective amount of a compound of Formula (Ia), (Ib), (II) or (III) and a pharmaceutically acceptable excipient, such as are described below.

As mentioned above, the compounds of the present invention are GI sparing NSAIDs. NSAIDs operate through the inhibition of COX I and COX II, the enzymes which catalyze the oxygenation and cyclization of arachidonic acid to prostaglandin H_2. COX I is expressed in most tissues, including the GI tract and the kidney, while COX II expression has been found in inflamed cells and tissues. We believe that specific and selective inhibitors of COX II can possess the desirable therapeutic effects of NSAIDs, such as anti-inflammatory action and some analgesic traits, without exhibiting adverse side effects to the GI tract and kidneys.

To find NSAIDs highly selective for COX II, compounds are screened and structure activity selectivity relationships defined. Determination of tertiary structure of enzyme inhibitor complexes also facilitates discovery of potent and selective inhibitors. An appreciable supply of purified human COX I and COX II was achieved with the expression of both human COX isoforms in a baculovirus expression system and purification of the enzymes to high levels, as described below in the examples, and also in Barnett, *et al.*, "Purification, Characterization and Selective Inhibition of Human Prostaglandin G/H Synthase 1 and 2 Expressed in the Baculovirus System", Biochemica Biophysica Acta, *in press* (1994). The purified enzymes can readily be obtained in milligram quantities. Furthermore, the recombinant enzymes have the properties of native enzymes and therefore, are suitable for discovery of selective COX II inhibitors.

Accordingly, this invention also pertains to a method of selecting NSAIDs that will not exhibit adverse GI and renal side effects, comprising the step of testing the drug for its ability to inhibit the enzyme activity of cyclooxygenase I and cyclooxygenase II, wherein selective inhibition of cyclooxygenase II over cyclooxygenase I is indicative of a GI and renal sparing drug. Preferably, this selective inhibition is at least 10-fold, preferably at least 100-fold.

NSAIDs can be tested for inhibition of COX I and COX II activity in any one of several assays that are well known in the art. One such assay is the radiometric assay described in Example 32, which involves the following steps: (1) the enzyme is activated by incubation with phenol and hematin, (2) the sample is combined with the activated enzyme, (3) the mixture is incubated, (4) radiolabeled substrate (arachidonic acid) is added, (5) the mixture in incubated, (6) the reaction is stopped, (7) the product is separated from the substrate, and (8) the product is counted, the level of radioactivity being related to the level of enzyme activity. An enzyme immunoassay can also be used to measure inhibition of COX I and COX II activity. It follows a similar procedure as the radiometric assay, except that the substrate is not radiolabeled and the product (PGE_2) is directly measured after the reaction is stopped. Another technique that can be used to measure inhibition of COX I and COX II activity is the oxygen-electrode assay, which follows steps (1) through (4) of the radiometric assay, at which point oxygen consumption is measured.

If the compound is significantly more selective for COX II than for COX I, it will have all the beneficial properties of an NSAID but will not exhibit the adverse effects commonly seen in NSAIDS. It is important to note however, that prodrugs may not be active against purified COX I or COX II in *in vitro* assays such as those described above. First, one must determine what active compound the prodrug is converted to *in vivo*. Then, the selectivity of the active compound can be measured in an *in vitro* assay.

Accordingly, the present invention also relates to a method of treating pain and inflammation without obtaining adverse GI and renal side effects, comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound that selectively inhibits cyclooxygenase II over cyclooxygenase I. As mentioned above, the compounds of the invention are NSAIDs that are GI sparing therapeutic agents. Many of the compounds of the present invention also selectively inhibit COX II over COX I. In particular, Compound (16) has been shown to be significantly more selective for COX II than currently available NSAIDs. Table 2 in Example 32 also lists examples of other compounds of the invention that have shown selectivity for COX II.

Another aspect of the invention relates to the treatment of the above conditions or diseases by the selective inhibition of cyclooxygenase by inhibiting COX II activity.

It is expected that the compounds of the present invention will also have utility as anti-cancer agents. In particular, it is b lieved these compounds may prevent metastasis of benign and partially transformed colon polyps, as this has been seen in other inhibitors of prostaglandin synthesis. See Moorghen, *et al.*, Acta Histochemica Suppementband. 39:195-199 (1990).

As mentioned above, the compounds of this invention are administered in a therapeutically effective amount. Administration of the active compounds and salts described herein can b via any of the accepted modes of administration for agents that serve similar utilities.

The level of the drug in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt%) basis, from about 0.01-99.99 wt% of the drug based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the drug is present at a level of about 1-80 wt%. The actual amount of the compound of Formula (Ia), (Ib), (II) or (III), i.e., the active ingredient, will depend upon numerous factors and will vary with the route and form of administration.

Generally, an acceptable daily dose is about 0.001-150 mg per kilogram body weight of the recipient per day, preferably about 0.1-75 mg per kilogram body weight per day, and most preferably about 5-20 mg per kilogram body weight per day. Thus, for administration to a 70 kg person, the dosage range would most preferably be about 350 mg to 1.4 g per day. A typical dosage regimen would be, for example, a 500 mg tablet twice daily or a 250 mg tablet taken more frequently.

Administration can be via any accepted systemic or local route, for example, via parenteral, oral (particularly for infant formulations), intravenous, nasal, transdermal or topical routes, in the form of solid, semi-solid or liquid dosage forms, such as for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, aerosols, emulsions or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical excipient and a compound of Formula (Ia), (Ib), (II) or (III) and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Excipients can be selected from the various oils, including those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. Other suitable pharmaceutical excipients and their formulations are described in "Remington's Pharmaceutical Sciences" by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

The compounds of the present invention can be administered by intravenous injection, for example, by dissolving the compound, salt, ester or ether in a suitable solvent (such as water or saline) or incorporation in a liposomal formulation followed, by dispersal into an acceptable infusion fluid. A typical daily dose of a compound of the invention can be administered by one infusion, or by a series of infusions spaced over periodic intervals.

Oral administration can also be used to deliver the compounds of Formula (Ia), (Ib), (II) and (III) using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. For such administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions preferably contain about 25-80 wt% of the active ingredient.

Preferably the compositions will take the form of a capsule, pill or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, polyvinylpyrrolidone, gum acacia, gelatin, cellulose and derivatives thereof, and the like. For oral administration to infants, a liquid formulation (such as a syrup or suspension) is preferred.

Pharmaceutical formulations based on liposomes have recently reached human clinical trials. Controlled release liposomal liquid pharmaceutical formulations for injection or oral administration are described in Suzuki, *et al.*, U.S. Patent No. 4,016,100. Liposomal applications for oral drug delivery of a lyophilized liposome/peptide drug mixture filled into intestine capsules have also been suggested, as in Horikoshi, *et al.*, U.S. Patent No. 4,348,384. The foregoing are incorporated herein by reference.

For systemic administration via suppository, traditional binders and excipients include, for example, polyalkaline glycol or triglycerides such as PEG 1000 (96%) and PEG 4000 (4%). Such suppositories may be formed from mixtures containing active ingredients in the range of about 1-2 wt%.

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound (about 1-20 wt%), as described abov , and optional pharmaceutical adjuvants in a excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

Actual methods of preparing such dosage forms ar known, or will be apparent, to those skilled in this art; for example, see "Remington's Pharmaceutical Sciences" *supra*. The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treated in accordance with the teachings of this invention.

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

ABBREVIATIONS

DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
CDI	Carbonyldiimidazole
EDTA	Ethylenediaminetetraacetic acid
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
FCS	Fetal calf serum
HOAc	Acetic acid
MeOH	Methanol
NaOAc	Sodium acetate
THF	Tetrahydrofuran
TLC	Thin layer chromatography

SYNTHESIS EXAMPLES

EXAMPLE 1

25 g of the commercially available sodium salt of zomepirac (Sigma), [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-acetic acid Na salt (1:1) [Compound (11)], was placed into 150 ml DMF, and 15 ml CH_3I was added and stirred at room temperature overnight. TLC indicated a slight amount of starting material. The mixture was then added to 700 ml H_2O and extracted with EtOAc (3x). The combined organic layers were washed 5x with H_20 and 1x with brine, dried and evaporated to a small volume. An approximately equal volume of hexane (~100 ml of each) was added, the mixture filtered, washed again with hexane, then air dried to yield 20.0 g [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-acetic acid methyl ester [Compound (12)].

40 g of Compound (12) was placed into 400 ml DMF, cooled to 0°C. To this mixture was added 45 g of 3,6-dichloropyridazine, and 11.4 g of 60% NaH in 4 portions about 10 minutes apart. When addition was complete, the mixture was removed from the ice bath. Forty-five minutes later, TLC indicated the presence of the starting material ester (no dichloropyridazine). An additional 5 g of 3,6-dichloropyridazine and 750 mg NaH were added and, after ~45 minutes, TLC indicted no ester. The mixture was added to 1400 ml H_2O containing 80 g $NaHSO_4$, extracted with EtOAc, washed 5x with H_2O, 1x with brine, dried, evaporated, and swirled with a small amount of hexane. The hexane was decanted and discarded. The residue was evaporated to yield [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-chloro-pyridazin-3-yl)-acetic acid methyl ester [Compound (13)]; m.p. 137.5-138°C.

Compound (13) was placed into 300 ml MeOH. To this mixture was added 100 ml H_2O and 11.2 g $LiOH \cdot H_2O$ and stirred at room temperature to yield [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-chloro-pyridazin-3-yl)-acetic acid Li salt (1:1) [Compound (14)].

After ~90 minutes, TLC indicated complete reaction. The mixture was added to a mixture of 1400 ml H_2O and 100 ml concentrated HCl (bubbling noted), and stirred for ~15-20 minutes. The mixture was filtered, the solid washed 2x with H_2O, then stirred with a mixture of 100 ml EtOAc and 200 ml hexane, again filtered, washed with hexane, then air dried to yield 41.2 g of the chloropyridazine compound, (4-Chloro-phenyl)-[5-(6-chloro-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (15)]; m.p. 157-159°C.

Compound (15) was placed into 200 ml HOAc, and 10 g NaOAc was added. The mixture was heated at reflux. After ~1 hour TLC showed no starting material. The mixture was removed from heat and added to 1500 ml H_2O. After stirring for ~15 minutes, the mixture was filtered, the solid was stirred with a mixture of ~200 ml acetone/100 ml hexane, filtered again, washed 2x with hexane, and then air dried to yield: 36.0 g of 6-[5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (16)]; m.p. 202-203°C.

EXAMPLE 2

3.24 g of Compound (15) from Example 1 was dissolved in DMF, followed by the addition of 430 mg of 60% NaH. The anion was allowed to generate for 30 minutes. To this was added 1.0 ml of CH_3I. After ~1 hour TLC showed that the reaction was complete. The mixture was added to H_2O, extracted with EtOAc. The organic layer was washed 5x with H_2O and 1x with brine, dried, then evaporated. The mixture was run on a silica gel column in 1:1 EtOAc:hexan (crude product absorbed onto silica gel) to yield 2.3 g of (4-Chloro-phenyl)-[5-[1-(6-chloropyridazin-3-yl)-ethyl]-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (17)].

Compound (17) was placed into 40 ml HOAc and 600 mg NaOAc was added. The mixture was heated at reflux. After ~90 minutes, TLC showed no starting material. The mixture was added to ~300 ml H_2O, stirred at room temperature for ~30 minutes, filtered, washed with H_2O, acetone, and hexane, then dried to yield 1.8 g of 6-[1-[5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-ethyl]-2H-pyridazin-3-one [Compound (18)]; m.p. 194.1-196.0°C.

EXAMPLE 3

720 mg of Compound (15) from Example 1 was placed into MeOH (20 ml). To this was added 540 mg $NaOCH_3$. The mixture was heated to reflux and after ~6 hours, TLC showed no starting material. Dichloromethane was added and the mixture absorbed onto silica gel and evaporated. The silica gel was loaded onto a silica gel column and eluted with 1:1 EtoAc:hexane to yield ~600 mg of product.

The product was stirred with EtOAc and hexane, filtered, and dried to yield 255 mg of (4-Chloro-phenyl)-[5-(6-methoxy-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (19)]; m.p. 152.5-153.5°C.

EXAMPLE 4

400 mg of 60% NaH was added to ~20-25 ml of isopropanol. The mixture was stirred at room temperature until all the NaH was consumed. To this gray sandy liquid was added 720 mg of Compound (15) from Example 1. This mixture was heated at reflux. After ~4 hours TLC showed that the reaction was complete. Dichloromethane was added to the mixture to complete dissolution. The mixture was purified as in Example 3, to yield 496 mg of (4-Chloro-phenyl)-[5-(6-isopropoxy-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (20)]; m.p. 124.9-126.3°C.

EXAMPLE 5

240 mg of Na was dissolved in EtOH and when all the Na was consumed, 720 mg of Compound (15) from Example 1 was added. The mixture was heated to reflux. After 4 hours, TLC showed no starting material.

The mixture was purified as in Example 3, to yield 421 mg of (4-Chloro-phenyl)-[5-(6-ethoxy-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (21)]; m.p. 132.8-133.7°C.

EXAMPLE 6

0.9 ml of morpholino ethanol was dissolved in THF and 400 mg of 60% NaH was added. The Na salt of morpholino ethanol was allowed to form. After all the bubbling had stopped, 720 mg of Compound (15) from Example 1 was added. The mixture was heated at reflux, followed by TLC. After ~3 hours, TLC showed no starting material. Dichloromethane was added, the mixture was absorbed onto silica gel and run on a silica gel column eluting with 95:5 dichloromethane:MeOH. The product from the column was dissolved in EtOAc, then made acidic with an excess of Et_2O/HCl and evaporated to give a solid. This was stirred with EtOAc, filtered and dried to yield 446 mg of (4-Chloro-phenyl)-[5-[6-(2-morpholin-4-yl-ethoxy)-pyridazin-3-ylmethyl]-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (22)]; m.p. 132.8-133.5°C.

EXAMPLE 7

1.025 g of Compound (16) from Example 1 was dissolved in DMF. To this was added 1.95 g Cs_2CO_3 (2 equivalents) and 0.19 ml CH_3I and the mixture was stirred at room temperature overnight under nitrogen. TLC indicated virtually complete reaction. The mixture was added to H_2O and extracted with EtOAc. The organic layer was washed 5x with H_2O and 1x with brine, dried and evaporated. This was purified on a silica gel column, eluting with 5% dichloromethane:MeOH to yield ~300 mg of Compound (23). This was recrystallized from acetone:hexane to yield 249 mg of 6-[5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2-methyl-2H-pyridazin-3-one [Compound (23)]; m.p.139.9-140.2°C.

EXAMPLE 8

2.72 g of Compound (16) from Example 1 was placed into a mixture of 240 ml of 1:1 THF:acetone. To this mixture, at ice bath temperatur , was added 1.68 g of 1,3-dichloro-5,5-dimethylhydantoin. The mixture was stirred at 0°C and followed by TLC, until the reaction was complete. The mixture was added to ~500 ml of 5% Na_2SO_3, extracted with dichloromethane, washed 1x with H_2O, dried and evaporated. The residue was stirred with EtOAc and filtered to yield 1.5 g of 6-[3-Chloro-5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (24)]; m.p. 247.2-248.5°C.

EXAMPLE 9

1.36 g of Compound (16) was placed into 120 ml 1:1 THF:acetone. This mixture was cooled to 0°C and 1.23 g of 1,3-dibromo-5,5-dimethylhydantoin was added. The mixture was stirred at ice bath temperature for ≈60 minutes. The mixture was added to a solution of 5% $NaSO_3$, extracted with dichloromethane, washed 2x with H_2O and 1x with brine, dried, and evaporated. The crude product was stirred with EtOAc, filtered, and dried to yield 1.33 g of 6-[3-Bromo-5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (25)]; m.p. 231.0-231.5°C.

EXAMPLE 10

4.0 g of Compound (13) from Example 1 was placed into 35 ml HOAc with 1.5 g NaOAc and heated at reflux. After ~90 minutes, TLC showed no starting material. The reaction was added to H_2O, the mixture filtered, and the solid was stirred with EtOAc/hexane, filtered, and dried to yield 3.5 g of [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid methyl ester [Compound (26)]; m.p. 216-217.5°C.

1.59 g. of Compound (26) was placed into 20 ml of MeOH. 12 ml of 0.98 M NaOH was added and the mixture was stirred at room temperature. After 2 hours TLC showed no starting material. The mixture was added to a solution of $NaHSO_4$ (5 g/300 ml), cooled, stirred for 20 minutes and filtered. The product was washed with hexane, stirred with acetone/hexane, and dried to yield 1.14 g of [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid [Compound (27)]. This compound was characterized as it sodium salt, [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid Na salt (1:1) [Compound (28)].

EXAMPLE 11

385 mg of Compound (27) from Example 10 was placed into MeOH. To this was added 84 mg of $NaHCO_3$ dissolved in the minimum amount of water. The mixture was stirred at room temperature for 10 minutes and evaporated to dryness to yield 355 mg of Compound (28); m.p. 189°C (effervesces).

EXAMPLE 12

385 mg of Compound (27) from Example 10 was placed into THF. To this was added 200 mg of CDI and 0.15 ml of morpholino ethanol. This mixture was stirred at room temperature overnight. TLC showed a mixture of [5-(4-Chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]-(6-oxo-1,6-dihydro-pyridazin-3-yl)-acetic acid 2-morpholin-4-yl ethyl ester [Compound (29)] and decarboxylated material, Compound (16). The mixture was added to H_2O, extracted with EtOAc, washed 1x with brine and 1x with H_2O, dried and evaporated. This was run on a silica gel column in 95:5 dichloromethane:MeOH. The product was dissolved in EtOAc, the solution was acidified with HCl/Et_2O, then evaporated to dryness. The residue was stirred with EtOAc, filtered and dried to yield 167 mg of Compound (29); m.p. 162.5°C (effervesces).

EXAMPLE 13

A solution of N,N,4-Trimethyl-benzamide [Compound (69)] (7.6 g, 0.05 mole) and $POCl_3$ (7.46 g, 0.048 mole) in dichloroethane (100 ml) was refluxed for 45 minutes, then cooled to room temperature and (1,4-Dimethyl-1H-pyrrol-2-yl)-acetic acid ethyl ester [Compound (70)] (5.0 g, 0.025 mole) in dichloroethane (20 ml) was added. The reaction was refluxed for 4 hours and then stirred at room temperature for 18 hours. A solution of NaOAc (4.5 g, 0.54 mole) in 200 ml of H_2O was added and the mixture refluxed for 2 hours. The two phases were separated, the aqueous extracted with dichloromethane (2x100 ml), the organics combined and dried over Na_2SO_4, and concentrated. The crude material was purified by column with FLORISIL® using 9:1 hexane:EtOAc to give 5.1 g (67% yield) of [1,4-Dimethyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-yl]-acetic acid ethyl ester [Compound (71)].

EXAMPLE 14

A solution of (1-Methyl-1H-pyrrol-2-yl)-acetic acid ethyl ester [Compound (73)] (2.0 g, 0.012 mole) and 4-Methoxy-benzoyl chloride [Compound (72)] (6.12 g, 0.036 mol) in 50 ml of xylene was refluxed for 60 hours. The solution was poured on a column of alumina and eluted with hexane followed by 9:1 hexane:EtOAc to give 2.0 g (56% yield) of [5-(4-Methoxy-benzoyl)-1-m thyl-1H-pyrrol-2-yl]-acetic acid ethyl ester [Compound (74)].

EXAMPLE 15

Oxo-(1H-pyrrol-2-yl)-acetic acid ethyl ester [Compound (75)] was synthesized by the procedure described in Behr, *et al.*, Acta Chem. Scan. 27:2411 (1973). A solution of Compound (75) (50 g, 0.29 mole) in 500 ml of acetone was cooled to 5°C with mechanical stirring. 1,3-dichloro-5,5-dimethylhydantoin (65.0 g, 0.32 mole) was added and the reaction allowed to reach 15°C. The reaction was stirred for 1 hour and poured into 1 liter of 10% $NaHSO_3$, extracted with EtOAc (3x300 ml), the organics combined and washed with H_2O (500 ml), dried over Na_2SO_4 (anhydrous) and concentrated. The crude material was purified by column on silica gel using 95:5 hexane:EtOAc to obtain 25 g (42% yield) of (4-Chloro-1H-pyrrol-2-yl)-oxo-acetic acid ethyl ester [Compound (76)].

To a solution of Compound (76) (10.0 g, 0.049 mole) in DMF (25 ml) was added K_2CO_3 (anhydrous) (8.25 g, 0.059 mole) at room temperature. After stirring for 1 hour, the suspension was cooled to 5°C, methyl iodide added (3.3 ml, 0.054 mole) and stirring continued for 3 hours. The reaction was poured into a cooled solution of 10% HCl (500 ml), extracted with EtOAc (3x500) and the organics washed with H_2O (5x100 ml), dried over Na_2SO_4 (anhydrous) and concentrated to give 14.0 g of crude product. This was purified on FLORISIL using 9:1 hexane:EtOAc to obtain 11.5 g (100% yield) of (4-Chloro-1-methyl-1H-pyrrol-2-yl)-oxo-acetic acid ethyl ester [Compound(77)].

To a suspension of $NaBH_4$ (14.8 g, 0.39 mole) in 100 ml of ethanol and 20 ml of H_2O at -78°C was added Compound (77) (28.0 g, 0.13 mole) in 500 ml of methanol. The reaction was allowed to reach -50°C and was stirred with a mechanical stirrer for 2 hours. Then the reaction was brought to pH=8 with HOAc:H_2O, concentrated, and the residue dissolved in EtOAc (300 ml). The organic phase was washed with H_2O, dried over Na_2SO_4 and concentrated to give (4-Chloro-1-methyl-1H-pyrrol-2-yl)-hydroxy-acetic acid ethyl ester [Compound (78)] as a white solid (26 g) that was used without purification in the next reaction.

To a solution of iodine (28.0 g, 0.11 mole) in 1 liter of benzene with mechanical stirring, was added PPh_3 (59.0 g, 0.22 mmole). After 10 minutes, a yellow solid was formed. The crude Compound (78) (26.0 g) was added as a solid and the reaction stirred for 3 hours at room temperature. The reaction was filtered through CELITE® and the volume was reduced to on third and this was applied to a column of FLORISIL and eluted with 9:1 hexane:EtOAc to obtain 14.0 g (54% yield, two steps) of (4-Chloro-1-methyl-1H-pyrrol-2-yl)-acetic acid ethyl ester [Compound (79)].

EXAMPLE 16

To a suspension of NaH/mineral oil 50% (10.8 g, 0.23 mole) in 20 ml of DMF, cooled in an ice bath, was added Compound (75) (See example 15) (25.0 g, 0.15 mole) in 50 ml of DMF. It was allowed to react for 2 hours at room temperature, then cooled in an ice bath and treated with ethyl iodide (23.99 ml, 0.3 mole). The reaction was stirred for 4 hours at room temperature then poured into a 10% HCl solution, cooled and the aqueous extracted with ethyl acetate (2x300 ml), and the combined organic phases washed with H_2O (5x300 ml), dried over Na_2SO_4 and concentrated. The crude material was purified on a column of FLORISIL eluted with 9:1 hexane:EtOAc to obtain 8.6 g (30% yield) of (1-Ethyl-1H-pyrrol-2-yl)-oxo-acetic acid ethyl ester [Compound (83)].

A solution of (1-Ethyl-1H-pyrrol-2-yl)-oxo-acetic acid ethyl ester [Compound (83)] (8.6 g, 0.044 mole) in 300 ml of MeOH was cooled to -70°C and $NaBH_4$ (5.0 g, 0.13 mole) was added. The reaction was stirred for 3 hours at -70°C, then neutralized to pH=8 with 1:1 HOAc:H_2O. The solvent was almost evaporated, and the residue dissolved in 300 ml of EtOAc, washed with H_2O (200 ml), dried over Na_2SO_4 and concentrated to give 9.0 g of (1-Ethyl-1H-pyrrol-2-yl)-hydroxy-acetic acid ethyl ester [Compound (84)] as a white solid that was used in the next reaction.

Compound (84) (9.0 g) was dissolved in 1,2-dichloroethane (50 ml). ZnI_2 (21.92 g, 0.07 mole) was added, followed by $NaBH_3CN$ (14.35 g, 0.23 mole) at room temperature. The reaction was stirred for 5 hours at room temperature then poured into ice water. The compound was extracted with EtOAc (250 ml), the organic phase washed with H_2O, dried over Na_2SO_4 and concentrated to obtain 7.2 g of crude product. This was purified on a column using FLORISIL and eluting with 9:1 hexane:EtOAc to obtain 2.0 g (24% yield, two steps) of (1-Ethyl-1H-pyrrol-2-yl)-acetic acid ethyl ester [Compound (85)].

EXAMPLE 17

6-[5-(4-Methyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (100)] was synthesized as d scribed in Example 1, using th commercially available sodium salt of tolmetin (Sigma), [1-Methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-yl]-acetic acid Na salt (1:1) [Compound (10)], as the starting material.

EXAMPLE 18

To a solution of Compound (100) from Example 17 (300 mg, 0.97 mmole) in 15 ml of acetone and 15 ml of THF at 5°C, was added 1,3-dichloro-5,5-dimethylhydantoin (192 mg, 0.97 mmole). The reaction was allowed to reach room temperature and after 1 hour, a additional 30 mg of 1,3-dichloro-5,5-dimethylhydantoin was added. After 10 minutes, the reaction was poured into a 5% $NaHSO_3$ solution and extracted with EtOAc (2x50 ml). The organic phase was washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The crude material was purified on preparative TLC (EtOAc) to obtain 161 mg (48% yield) of 6-[3-Chloro-5-(4-methyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (87)]; m.p. 212-214°C.

EXAMPLE 19

A suspension of Compound (100) from Example 17 (1.5 g, 4.9 mmole) and activated Zn (0.96 g, 14.6 mmole) in 25 ml of HOAc was refluxed for 3 hours with vigorous stirring. The reaction was filtered through CELITE and the residue washed with dichloromethane. The solution was evaporated and the solid (1.55 g) crystallized (EtOAc) to give 774 mg (51% yield) of 6-[5-(4-Methyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-4,5-dihydro-2H-pyridazin-3-one [Compound (102)] as crystals; m.p. 171-172°C.

EXAMPLE 20

6-[5-(4-Bromo-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (57)] was synthesized according to the method described in Scheme A, Steps 1-4a.

A solution of Compound (57) (0.4 g, 0.011 mole), trimethylsilylacetylene (excess), palladium diacetate (24 mg, 0.1 mmole) and PPh_3 (47 mg, 0.18 mmole) in triethylamine (6 ml) and acetonitrile (3 ml) was refluxed for 4 hours under argon. The reaction was concentrated and the crude purified on flash chromatography (EtOAc) to give 6-[1-Methyl-5-[4-(2-trimethylsilanyl-ethynyl)-benzoyl]-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (61)] (380 mg, 90% yield).

A suspension of Compound (61) (365 mg, 0.94 mmole) and K_2CO_3 (30 mg) in methanol (10 ml) was stirred for 2.5 hours at room temperature. The solvent was removed and the residue purified by flash chromatography (silica gel) using EtOAc to obtain 6-[5-(4-Ethynyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one [Compound (65)] (184 mg, 62% yield); m.p. 185-187°C (hexane:acetone).

EXAMPLE 21

[1-Methyl-5-(4-nitro-benzoyl)-1H-pyrrol-2-yl]-acetic acid methyl ester [Compound (104)] was synthesized according to the method described in Scheme A, Step 1.

A solution of Compound (104) (2.5 g, 8.3 mmole), Ni_2B (2.5 g) and 1 M HCl (35 ml) in methanol (140 ml) was placed in an oil bath at 65°C for 30 minutes. The reaction was brought to basic pH with concentrated NH_4OH, extracted with EtOAc and the organic extracts dried over Na_2SO_4 and evaporated. The crude extract was purified by column (6:4 hexane:EtOAc) to obtain the desired aniline product (2.03 g, 90% yield).

The aniline product (2.2 g, 8.1 mmole) and acetic anhydride (25 ml) in pyridine (50 ml) was stirred at room temperature for 18 hours. The reaction was concentrated and azeotroped with toluene to give the crude [5-(4-Acetylamino-benzoyl)-1-methyl-1H-pyrrol-2-yl]-acetic acid methyl ester [Compound (105)] as a white solid (2.35 g) which was used in subsequent reactions without purification.

EXAMPLE 22

5.0 g of Compound (15) from Example 1 was suspended in 14 ml anhydrous hydrazine and 2 ml of n-butanol. The reaction was heated to reflux, at which time the solid dissolved and the reaction was homogeneous. After 1 hour of reflux TLC (20% ethyl acetate/hexane) indicated that all of the starting material had been consumed. The reaction was cooled to room temperature, at which time a precipitate formed. The reaction was filtered, the solid washed 2x with water, 2x with ether and placed under vacuum (approximately 0.1 mm Hg) for 3 hours to give 5.45 grams (>100%). 2.0 g of this solid was recrystallized from water/DMSO to give 1.45 g of (4-Chloro-phenyl)-[5-(6-hydrazino-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (96)]. The rest of the material was used as obtained in further reactions.

300 mg of Compound (96) was suspended in 20 ml absolute methanol, and approximately 500 mg Raney Nickel (washed 3x with methanol) was added as a suspension in methanol (3 x 2 ml). The mixture was heated at reflux for 2 hours. The reaction was cooled, filtered through a glass filter pad and rotovaped to give a yellow solid. Recrystallization (CH_3CN/DMF/water) gave 215 mg of [5-(6-Amino-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-(4-chloro-phenyl)-methanone [Compound (103)]; m.p. 206.8-209°C. Theoretical: C, 63.44; H, 5.03; N, 16.44. Found: C, 63.26; H, 4.98; N, 16.53.

EXAMPLE 23

500 mg of Compound (15) from Example 1 was dissolved in 3 ml absolute ethanol. 127 mg of thiourea (1.2 eq., 1.67 mmol) was suspended in this mixture, and the reaction was heated to reflux. The solution became homogeneous at reflux, followed by formation of a precipitate after about 15 minutes. The reaction was heated for a total of 45 minutes. TLC (20% ethyl acetate/hexane) showed no change, however the precipitate had stopped forming at this point. The reaction was cooled and the ethanol removed in vacuo. To this solid was added a solution of 147 mg sodium carbonate (1 eq., 1.39 mmol) dissolved in 1 ml water. The reaction was stirred for 15 minutes, filtered, the solid residue obtained was then washed with water and ethanol. Recrystallization (acetone/hexane) gave 275 mg of an olive green solid, (4-Chloro-phenyl)-[5-(6-mercapto-pyridazin-3-ylmethyl)-1,3-dimethyl-1H-pyrrol-2-yl]-methanone [Compound (169)]; m.p. 220.4-222.4°C. Theoretical: C, 60.41; H, 4.51; N, 11.74. Found: C, 60.15; H, 4.34; N, 11.80.

EXAMPLE 24

As mentioned above, Compound (16) has been found to exist in at least three crystal forms (Phase I, Phase II and Phase III) and two hydrates (Hydrate I and Hydrate II).

Phase I was obtained when Compound (16) was recrystallized from methanol, ethanol, ethanol/acetic acid, acetone, ethyl acetate, ethyl acetate/acetic acid, dichloromethane, tetrahydrofuran or tetrahydrofuran/ethyl acetate. Unmilled Phase I (~200 μm) was found to be physically stable at 40°C/75% relative humidity for at least 4 days. Milling and micronization did not cause any phase transformation. When suspended in water, Phase I converted to a monohydrate, Hydrate I. Hydrate I can be converted back to Phase I by suspension in alcohol.

Phase II was obtained when Compound (16) was recrystallized from toluene. When suspended in water, Phase II was converted to another hydrate, Hydrate II. When suspended in alcohol or ethyl acetate, Phase II converted to Phase I.

Phase III was obtained by rapid precipitation of Compound (16) from acetic acid/water. When suspended in water, Phase III converted to Hydrate I. When suspended in alcohol, Phase III converted to Phase I.

Hydrate I, a monohydrate, was also obtained by slow recrystallization of Compound (16) from acetic acid/water. Hydrate I was found to be physically stable at 40°C/ambient relative humidity, within the range of 11-95% relative humidity, and 40°C/75% relative humidity (14 days). Dehydration at temperatures below 100°C produced a metastable form that converted back to Hydrate I at ambient conditions and 23% relative humidity. Heating Hydrate I at 120°C caused a phase conversion to another anhydrous crystal form.

Based upon their characteristics and physical properties, both Phase I and Hydrate I were selected for further evaluation in bioavailability and formulation studies.

FORMULATION EXAMPLES

The following examples illustrate the preparation of representative pharmaceutical formulations containing Compound (16) as the active ingredient. Other compounds of Formula (Ia), (Ib), (II) and (III), such as those prepared in accordance with Examples 1-23, can be used as the active ingredient in preparation of the formulations of these examples.

EXAMPLE 25

This example illustrates the preparation of a representative pharmaceutical formulation for oral administration containing Compound (16). Compound (16) and povidone were combined in a weight ratio within the range of 1:0.5 to 1:5 to form a solid dispersion. Compound (16) and povidone were first dissolved in HOAc at 80°C then evaporated quickly at 110°C, under vacuum. The remaining material was then introduced into a hard-shell gelatin capsule or Syntex Suspension Vehicle ("SSV"; 0.9% NaCl, 0.5% sodium carboxymethylcellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol and 97.3% distilled water).

The process used in this example, along with that described in Example 26 creates a homogeneous material made up of relatively small crystals and/or amorphic state of drug uniformly dispersed through out a soluble matrix. Dissoluti n studies in water showed that this matrix promotes rapid initial release of the drug.

Compound (16) and povidone can also be dissolved in other solvents such as ethanol, methylene chloride and ethanol:methylene chloride.

EXAMPLE 26

This example illustrates the pr paration of another representative pharmaceutical formulation for oral administration, containing Compound (16). Compound (16) and citric acid were combined in a weight ratio within the range of 1:1.2 to 1:1.5 to form a solid dispersion. Compound (16) was melted in citric acid at 165°C to dissolve the drug, then chilled on an ice bath. The remaining material was then introduced into a hard-shell gelatin capsule or SSV.

EXAMPLE 27

This example illustrates the preparation of another representative pharmaceutical formulation for oral administration containing the active compound, Compound (16), where:

Ingredient	Quantity per tablet, mg
active compound	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

EXAMPLE 28

This example illustrates the preparation of another representative pharmaceutical formulation containing the active compound, Compound (16). A suspension for oral administration is prepared having the following composition:

Ingredient	Amount
active compound	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

where "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to a desired volume such as 100 ml.

EXAMPLE 29

This example illustrates the preparation of a representative injectable pharmaceutical formulation containing the active compound, Compound (16). Th injectable preparation, buffered to a suitable pH, is prepared having the following composition:

Ingredient	Amount
active compound	0.2 g
sodium acetate buffer solution, 0.4 M	2.0 ml
HCl (1N) or NaOH (1N) q.s.	to suitable pH
water (distilled, sterile)	q.s. to 20 ml

EXAMPLE 30

This example illustrates the preparation of a representative pharmaceutical formulation for topical application containing the active compound, Compound (16), where:

Ingredient	Amount, g
active compound	0.2-10
Span 60	2
TWEEN®60	2
mineral oil	5
petrolatum	10
methyl paraben	0.15
propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60-70°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

EXAMPLE 31

This example illustrates the preparation of a representative suppository pharmaceutical formulation containing the active compound, Compound (16). A suppository totalling 2.5 grams is prepared with witepsol (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York) and has the following composition:

active compound	500 mg
witepsol H-15	balance

TESTING EXAMPLES

The anti-inflammatory and analgesic activity of the compounds of the invention can be determined by a variety of assays utilizing both *in vitro* and *in vivo* procedures, such as by following, for example, th pr cedur s described in the examples below, or modifications thereof. In this manner, the potency and selectivity of compounds useful as NSAIDs can be determined.

Materials

Human prostaglandin G/H synthase I and II ("COX I" and "COX II") were expressed in the baculovirus expression system and purified to high levels. Both enzymes were glycosylated and possessed both cyclooxygenase and peroxidase activities. Transplacement plasmid construction

A 2 Kb fragment containing the coding region of COX I (Oxford Biomedical Research, Inc. Oxford, MI) was cloned into the plasmid pBS (Stratagene, La Jolla CA). The fragment was released from the resulting plasmid, pBS/COX I_{hum}, by digesting with XhoI and SspI and then isolated by agarose gel electrophoresis. The resulting fragment contained, in addition to the coding sequence for COX I, the 5' flanking sequence, CTCGATG, and 160 bp of the 3' noncoding sequence. The fragment was purified using Elu-Quik (Schleicher & Schuell, Inc., Keene, NH) following the manufacturer's protocol, then ligated into the XhoI-SmaI sites of pSyn XIV VI*X3, Wang, *et al.*, Gene 100:131-137 (1991). The resulting transfer vector was designated "pCOX I".

A 1.8 Kb DNA fragment containing the coding region of human COX II was generated by PCR using pcDNA/COX II (Hla, *et al.*, Proc. Natl. Acad. Sci. USA 89:7384-7388 (1992)) as the template, GAATTCTAAATATG CTCGCCCGCGCCCTGCTG as the 5' primer and ATTAGACTTCTACAGTTCAGTCGAAC as 3' primer. These primers were designed to amplify the coding sequence for COX II with TAAAT, a sequence that gives optimal translation of very late baculovirus genes (Matsuura, *et al.*, J. Gen. Virol. 68:1233-1250 (1987)), juxtaposed to the initiation codon of the COX II gene. The template was denatured at 94°C for 1 minute, the primers allowed to anneal at 55°C for 2 minutes and the extension reaction was at 72°C for 3 minutes. Thirty cycles of amplification were completed. The resulting 1.8 Kb DNA fragment was digested with EcoRI and BglII and cloned into EcoRI/BglII digested pSyn XIV VI*X3. Several clones were sequenced and one that contained the correct sequence was selected and designated "pCOX II".

Generation of recombinant virus

A DNA solution consisting of 0.5 µg baculovirus virion DNA (Baculogold®, PharMingen, San Diego, CA) and 5 µg transplacement plasmid DNA (COX I or COX II) in HBS (20 mM Hepes, 150 mM NaCl, pH 7.4) was prepared. Immediately prior to transfecting Sf9 baculovirus cells, 1.5 ml of the DNA solution was mixed with an equal volume of lipofectin (0.67 µg lipofectin/ml HBS), Felgner, *et al.*, (1987) Proc. Natl. Acad. Sci. 84:7413-7417 (1987). Sf9 cells in Ex-Cell 400 media (JRH Scientific, Woodland, CA) were seeded into T-25 flasks ($3x10^6$ cells/flask). After approximately 1 hour, when the cells had attached to the flask, the medium was decanted and the cell monolayer washed with HBS. 3 ml of the lipofectin-DNA mixture was then layered over the cells. After 40 minutes at 28°C, 3 ml of Ex-Cell 400 supplemented with 10% FCS and gentamicin (50 µg/ml) were added to the flask to dilute the lipofectin-DNA solution. After 30 minutes the lipofectin-DNA solution was replaced with fresh Ex-Cell 400 (with 2.5% heat inactivated FCS). Five days later the supernatant was collected and clarified by centrifugation (800 x g, 15 min). Ten-fold serial dilutions of the clarified supernatant in Ex-Cell 400 were then prepared. Sf9 cells were seeded in 6 well plates at a density of $0.8x10^6$ cells/well. When the cells attached, the medium was decanted and 0.5 ml of the serially diluted culture fluid from transfected cells was gently pipetted onto the monolayers. The cells were incubated at room temperature with gentle agitation every 15 minutes. After 1 hour, the virus inocula were aspirated and the cells overlayed with 2 ml ExCell 400 containing 1.5% melted agarose. Five days later an additional 2 ml Ex-Cell 400-agarose containing 3% neutral red was layered over the first agarose overlay. The next day, unstained plaques were counted to determine the virus titer. Well separated plaques were picked and aspirated into 1 ml medium which was then inoculated onto Sf9 monolayers in 6 well plates. Three days later, when most cells contained polyhedra, the cells were harvested and assayed for COX activity. Virus in the culture fluid from cells expressing either COX I or COX II were designated vCOX I and vCOX II respectively and used as virus seed for production of the enzymes.

Production of COX I and COX II

In order to produce high levels of COX I and COX II, 9.5 liters of Sf9 cells growing exponentially in bioreactors were infected with either vCOX I or vCOX II at a multiplicity of infection of 0.5 plaque forming units per cell. At the time of infection, the cultures were fed 400 ml of a nutrient solution consisting of glucose, glutamine, yeastolate, and lipids, Nguyen, *et al.*, J. Biotechnol. 31:205-217 (1993). The cells were harvested by centrifugation three days later. The pellets w r stored frozen at -80°C until needed for purification of COX I and COX II.

Purification of COX I

Pellets of cells infected with vCOX I were thawed in chilled, deoxygenated lysis buffer (5 mM Tris, pH 8, containing 1 µg/ml pepstatin, 1 µg/ml leupeptin, 1 mM pefabloc SC (Pentapharm AG, Basel, Switzerland) and 10% glycerol). 5 ml of buffer was utilized for each $1x10^8$ cells lysed. The cells were disrupted. Centrifugation at 800 x g for 10 minutes pelleted nuclei and other d bris which wer extracted once again in half th original lysis buffer. Microsomes from the 800 x g supernatant were pelleted by centrifugation (105,000 x g, 1 hour). The pellet was suspended in solubilization buffer (5 mM Tris, pH 8, containing 1 µg/ml pepstatin, 1 µg/ml leupeptin, 1 mM pefabloc SC) by sonication. 5 ml of buffer was utilized for each $2x10^8$ cells lysed. One volume of 2% (w/v) TWEEN®20 (polyoxyethylenesorbitan monolaurate, Atlas Chemie G.m.b.H.) in solubilization buffer was added to each volume of suspended microsomes which were solubilized by gently rocking at 4°C for 1.5 hours. Insoluble debris was then removed by centrifugation (105,000 x g, 1 hour). The solubilized COX I was filtered through a 0.45 µm pore size filter and diluted with 1 volume of buffer used to equilibrate the ion-exchange column. An anion-exchange HPLC column (Bio-Gel, DEAE, 5-PW, 150 X 21.5 mm, BioRad Inc., Richmond CA) was equilibrated against mobile phase A (5 mM Tris, pH 8, 0.1% TWEEN 20, 10% glycerol). Solubilized COX I from $8x10^8$ cells was loaded onto the column which was then washed with mobile phase A until the UV absorbance (at 280 nm) returned to baseline (8 ml/min flow rate). Retained proteins were then eluted with a linear NaCl gradient to 0.4 M over a 40 min interval. The salt concentration was then increased to 1 M in 10 additional minutes. Fractions containing enzyme activity (radiometric assay method) were pooled and diluted with 3 volumes of Tris buffer (20 mM Tris, pH 7.5 containing 0.5 M NaCl) for further purification. A column packed with lentil lectin sepharose 4B (Pharmacia, Piscataway, N.J.) was equilibrated against Buffer A (20 mM Tris pH 7.5, 0.5 M NaCl, 0.02% TWEEN 20). Typically a 2.5 cm diameter column was packed to a bed height of 4.5 cm (0.8 ml/min flow rate). Pooled fractions from the ion-exchange column containing COX I were then loaded onto the column which was washed with Buffer A until the UV adsorption at 280 nm returned to baseline. The retained proteins were then eluted with an 18 minute gradient against Buffer B (buffer A + 0.5 M alpha-methylglucoside). The column was washed for 62 more minutes until all proteins had eluted. Fractions were assayed for enzymatic activity and the fractions containing COX I were pooled for further processing. The COX I from the lectin column was concentrated approximately 8 fold using a Centriprep 30 (Amicon, Danvers, MA). Up to 0.5 ml of the concentrated sample was injected into a gel filtration column (SPD X 75, HR 10/30, 1 X 30 cm). The mobile phase was 50 mM Tris pH 7.5, 0.1% TWEEN 20 (0.5 ml/min flow rate). COX I was found in the excluded volume at 11 minutes, while smaller molecular weight contaminants were washed through the column in 29 minutes. The purified enzyme was stored frozen at -80°C until needed.

Purification of COX II

COX II was extracted from pellets of cells infected with vCOX II and purified in a manner similar to COX I with a few exceptions: (1) diethyldithiocarbamate (100 µM) was added for the disruption buffer, but glycerol was omitted; (2) dodecylmaltoside (2.5%) was substituted for TWEEN 20 in the solubilization buffer; (3) the 0-40% B ion-exchange gradient was reduced to 20 minutes; (4) the ion-exchange pool was not diluted prior to loading on the lectin column; (5) the loading mobile phase of the lectin column was 20 mM Tris-HCl pH 8.0, 0.2 M NaCl, 0.1% octylglucoside; and (6) the mobile phase of the gel-filtration step was 50 mM Tris pH 8 plus 0.1% octylglucoside and the flow rate was 0.75 ml/min.

EXAMPLE 32

Enzymology: Activities Against COX I and COX II

As described above, human recombinant COX I and COX II were cloned and expressed in a baculovirus system. Partially purified COX I and COX II enzymes were used for screening compounds for their ability to inhibit COX I and COX II activity, as described below.

Compound (16), in 2 µl DMSO, and control samples (carrier vehicles only) were mixed with COX I or COX II samples (e.g. fractions from the chromatography columns) in polypropylene tubes and preincubated with 2 mM phenol for 5 minutes and then with 1 µM hematin for an additional 5 minutes. The 150 µl reaction mixture consisted of 50 mM Tris-HCl, pH 7.9, 2 mM EDTA, 10% glycerol, 200 µM phenol, 1 µM hematin, 1-25 µl sample and 20 µM 1-[^{14}C]arachidonate (80,000-100,000 cpm/tube). After 45 seconds at room temperature, the reaction was terminated by adding 200 µl of 2 N HCl and 750 µl water. An aliquot (950 µl) of the reaction mixture was loaded onto a 1 ml C_{18} Sep-Pak (J.T. Baker, Phillipsburg, NJ) which had been previously washed with 2-3 ml methanol and equilibrated with 5-6 ml distilled water. Oxygenated products were quantitatively eluted with 3 ml of acetonitrile, H_2O and acetic acid (50:50:0.1, v/v) and the radioactivity in the eluate determined in a scintillation counter.

In this radiometric assay, Compound (16) was shown to be highly selective for COX II (IC_{50} = 0.58-0.90 µM). By contrast, Compound (16) was essentially devoid of activity against COX I (IC_{50} > 1000 µM, over three assays). Compound

(16) displayed potent, time-dependent, reversible inhibition of COX II. At very low substrate concentration, Compound (16) displayed weak, competitive, non-time dependent inhibition of partially purified COX I.

With human foreskin fibroblasts incubated with Interleukin 1 and phorbol myristate acetate to induce expression of COX II, Compound (16) inhibited the producti n of PGE_2 elicited by calcium ionophor stimulation, with an IC_{50} = 0.12 μM. In washed human platelets stimulated with calcium ionophore to activate constitutive COX I, Compound (16) inhibited thromboxane B_2 production with an IC_{50} = 2.3 μM. In human whole blood activated with ionophore (COX I) or lipopolysaccharide (COX II), Compound (16) inhibited TxB_2 production with IC_{50} = 5.6 μM and 4.7 μM, respectively. The corresponding values for indomethacin in human whole blood are 0.13 μM and 1.7 μM.

A summary of activities of Compound (16) against COX I and COX II in cell-free enzyme preparations and whole cells is presented in Table 1. The following abbreviations are used: AA is arachidonic acid, IL-1 is interleukin 1, PMA is phorbol myristate acetate, A23187 is a calcium ionophore (Sigma), BSA is bovine serum albumin and LPS is a lipopolysaccharide (Sigma).

Table 1

Enzyme Source	Assay Conditions	COX I IC_{50}, μM	COX II IC_{50}, μM
Human recombinant -baculovirus -partially purified	10 min incubation with Compound (16) 45 sec incubation with 20 μM AA Separation of radioactive products	> 1000 > 1000 > 1000	0.58 0.90 0.64
Human foreskin fibroblasts -16 hr stimulation with IL-1 and PMA -washing, transfer to fresh media	30 min incubation with Compound (16) 10 min activation with a) 5 μM A23187 b) 20 μM AA + FA-free BSA EIA determination of PGE_2		a) ≤0.1 b) ≈2.7
Human foreskin fibroblasts -6 hr stimulation with IL-1 and PMA -washing, transfer to fresh media	30 min incubation with Compound (16) 10 min activation, 5 μM A23187 RIA determination of PGE_2		0.12 0.17 0.14
Human monocytes -freshly isolated *-These cells may be expressing COX II constitutively*	30 min incubation with Compound (16) a) 10 min activation, A23187 + PMA b) 30 min activation, A23187 +PMA c) 10 min activation, 20 μM AA d) 30 min activation, 20 μM AA EIA determination of PGE_2	a) 5.20 b) 0.31 c) 4.60 d) > 10	
Human adherent monocytes -18 hr stimulation with LPS -washing, transfer to fresh media	30 min incubation with Compound (16) a) 10 min activation, A23187 + PMA b) 30 min activation, A23187 +PMA c) 10 min activation, 20 μM AA d) 30 min activation, 20 μM AA EIA determination of PGE_2		a) 0.2 b) < 0.1 c) 2.8 d) 0.54
Washed human platelets	30 min incubation with Compound (16) a) 10 min activation, A23187 b) 10 min activation, 20 μM AA EIA determination of TxB_2	a) 2.3 b) > 100	
Human whole blood	30 min incubation with Compound (16) 15 min activation, A23187 EIA determination of TxB_2	3.0	
Human whole blood -30 min assay for COX I -5 hr assay for COX II	COX I- 15 min incubation with Compound (16); 30 min with A23187 COX II- 5 hr incubation with Compound (16) and 10 μg/ml LPS RIA determination of TxB_2	5.6 (3.8-7.3)	4.56 (4.36-4.80)
Rat whole blood	15 min incubation with Compound (16) 30 min activation with A23187 EIA determination of TxB_2	6 5 4	

Numerous other compounds of the invention were evaluated under the radiometric assay conditions described above using human recombinant baculovirus expressed enzymes. As with Compound (16), these compounds also exhibited COX II selectivity, as can be seen below:

Table 2

Compound #	COX I IC_{50}, μM	COX II IC_{50}, μM
9	>100	0.63
18	15	1.5
24	440	0.7
25	277	1.8
30	40	0.5
31	35	0.2
32	26.7	1.5
33	31.7	0.44
35	86	0.1
36	38	0.4
42	82	0.72
43	23	0.3
46	>100	7.2
53	420	1
54	190	0.44
57	700	4.6
62	140	7
80	≥1000	0.7
81	>300	0.44
82	20.6	0.81
87	>1000	0.9
88	100	0.55
89	8.1	2.3
95	140	1.3
100	300	1.5
102	260	3.1
107	21	2.3

114	82	0.66
116	0.92	0.18
118	76	0.8
120	8.9	0.8
121	6.3	0.23
122	0.074	0.063
123	3.5	<0.03
124	94	0.54
125	<10	1.6
126	61.4	0.97
127	57	0.67
129	3.4	0.067
130	>100	0.58
131	5.3	0.12
133	3.7	0.07
135	52	0.35
136	829	3.06
140	48	0.53
141	4.9	.125
142	67	4.16
144	1	0.59
145	85	0.91
148	81.4	0.66
151	3.8	<0.1
152	10	0.14
153	>100	0.54
156	89	0.52
157	24.4	1.63
158	3.2	0.68
161	64.7	0.61
168	7.9	0.91

EXAMPLE 33

Anti-inflammatory Activity

Carrageenan-induced paw edema in the rat has been used as the primary in vivo screen for anti-inflammatory activity of most NSAIDs. In this assay, NSAIDs typically produce a maximum inhibition of about 60%; therefore, the ED_{30}, which is the dose giving half-maximal inhibition, is the value reported.

Over a series of assays, in which Compound (16), suspended in SSV, was administered orally to rats 1 hour prior to injection of carrageenan, Compound (16) inhibited carrageenan-induced paw edema (ED_{30} = 1.1 ± 1.0 mg/kg).

Analysis of the data indicated that Compound (16) at the appropriate dose is capable of giving ~60% inhibition, the maximum amount achievable with NSAIDs.

Compound (16) was also tested in adjuvant-induced arthritis in the rat by dosing orally bid for 17 days beginning on the day of adjuvant injection. In a first test (0.1-5 mg/kg/day), Compound (16) gave 31% and 66% inhibitions at doses of 2 and 5 mg/kg/day, respectively. In a second test, 2, 5 and 10 mg/kg/day gave 43%, 48% and 52% inhibition, respectively, whereas indomethacin at 0.3 and 0.6 mg/kg/day gave 66% and 79% inhibition, respectively. In a third test at 1-100 mg/kg, Compound (16) produced dose dependent inhibition with a maximum of 80% inhibition at 100 mg/kg. Based on the data from thee three assays, Compound (16) has an ED_{40} = 3.2 ± 2.6 mg/kg.

Numerous other compounds of the invention were evaluated in a manner similar to Compound (16) and exhibited similar anti-inflammatory activity. These include Compounds (9), (18), (23) to (25), (29), (30), (32) to (35), (42), (43), (47), (53), (54), (80), (81), (95), (102), (112), (114), (116), (118), (120), (122) to (125), (127), (128), (140) to (142), (144), (145), (149), (152), (153), (161) and (169).

EXAMPLE 34

Analgesic Activity

Analgetic activity is determined by the Phenylquinone-induced Mouse Writhing Assay, Hendershot, *et al.*, J. Pharmacol. Exp. Ther., 125:237-240 (1959). This assay is one of several acute assays which have been used to assess the analgesic activity of NSAIDs. At the appropriate time after test material administration, phenylquinone is injected intraperitoneally to mice, inducing a series of characteristic "writhing" responses, which are counted between 10 and 20 minutes after phenylquinone injection.

In this assay, Compound (16), suspended in SSV, was tested over the dose range of 1-100 mg/kg administered 20 or 60 minutes prior to phenylquinone challenge. Compound (16) gave 100% inhibition at 100 mg/kg and the $ED_{50} \approx 10$ mg/kg.

Compound (16) was also evaluated using an adjuvant-induced arthritis pain model in the rat, in which pain is assessed by eliciting a vocal response upon squeezing or flexing an inflamed ankle joint. A preliminary test of Compound (16) at 0.1, 1.0, 10 and 30 mg/kg showed that significant and prolonged analgesia is obtained at doses _10 mg/kg.

Numerous other compounds of the invention were evaluated in a manner similar to Compound (16) and exhibited similar analgesic activity. These include Compounds (18), (34), (35), (122) and (153).

EXAMPLE 35

Gastrointestinal Erosive Activity

NSAIDs such as indomethacin are highly corrosive to the stomach and intestines of rats, and at relatively low doses administered sub-chronically (4-7 days), can cause erosions of the small intestine leading to frank ulceration, perforation and death due to peritonitis. For standard NSAIDs, the dose response is very steep with the lethal dose being only 4-5 fold that of the lowest dose producing minimal lesions, i.e., superficial mucosal damage.

When administered orally bid to rats for 4 days, Compound (16), suspended in SSV, caused no intestinal lesions at 25 mg/kg/day, and produced minimal lesions at 50 mg/kg/day (1 of 5 rats had a score of 1 on a scale of 0-5).

At 200 mg/kg/day, Compound (16) produced lesions in 4 of 5 rats, but the scores were no greater than 1. Lesions of this degree were detected by close observation of the entire length of the mucosal surface of ileum under appropriate reflected lighting conditions.

For a given ulcerogenic dose of drug, lesion intensity generally increases with duration of drug. Remarkable, no intestinal lesions were observed in the toxicology range-finding study in which rats were dosed with up to 300 mg/kg/day of Compound (16) for 14 days.

Num rous other compounds of the invention were evaluated in a manner similar to Compound (16) and exhibited similar GI erosive activity. These include Compounds (18), (95), (122) and (123).

EXAMPLE 36

In Vivo Inhibition of Eicosanoid Synthesis

To examine the effect of Compound (16) on prostaglandin (PG) synthesis in inflamed tissues, Compound (16) was tested in a carrageenan-induced inflammation (air-pouch model) in rats. PGE_2 levels in th air-pouch exudate were measured by enzyme immunoassay in rats treated with 0.1-30 mg/kg of Compound (16). Relative to a vehicle treated control group, Compound (16) dose-dependently inhibited PGE_2 levels in the exudate with an $IC_{50} \approx 0.7$-2 mg/kg. The NSAID indomethacin at 2-5 mg/kg also inhibited PGE_2 in the exudates to >70%.

To test the effects of Compound (16) on PG synthesis in non-inflamed tissue, PGE_2 levels were measured in the stomach of rats from the above experiments. Compound (16) at any of the concentrations tested (0.1-30 mg/kg had no significant inhibition of stomach PGE_2, while indomethacin at 2-5 mg/kg caused >80% inhibition of stomach PGE_2.

Numerous other compounds of the invention were evaluated in the above manner for the inhibition of PG synthesis in inflamed and non-inflamed tissues and exhibited similar activity. These include Compound (9), (35), (122), (123), (129), (145), (149), (153) and (161).

EXAMPLE 37

Pharmacokinetics

The pharmacokinetics of Compound (16) was studied in rat and monkey after intravenous and oral administration in solution (ethanol/polyethylene glycol/water, 1/5/4) or SSV.

Compound (16) was shown to have good bioavailability in rats and monkeys (40-80%). The compound also exhibited dose proportionality over a broad range of doses (1-300 mg/kg) and has a half-life of 2-3 hours after intravenous dosing.

EXAMPLE 38

Subchronic Toxicity

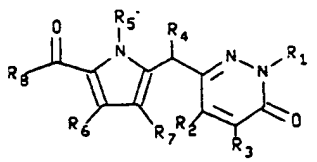
A two week range finding study in rats was carried out at daily doses of 10, 30, 100 and 300 mg/kg of Compound (16). All animals survived the study and no adverse clinical signs were noted. No clinical chemistry abnormalities were detected and there were no drug-related gross necropsy findings. In particular, no lesions were noted in the stomach or intestines. There were no histopathological findings.

A two week range finding study in cynomolgus monkeys was carried out at daily doses of 10, 30, 100 and 300 mg/kg of Compound (16). No abnormalities were observed in clinical signs, clinical chemistry, gross pathology or histopathology.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims

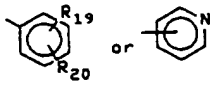
1. A compound having the structure:



wherein:

R_1 is -H, lower alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyl xy, substituted acyloxy, lower dialkylamino, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alken ,

lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

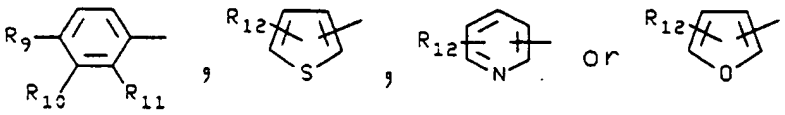
R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio; and

R_8 is:



where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; or pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein R_1, R_2, R_3, R_4 is -H; R_6 is -H or lower alkyl, R_7 is -H; R_8 is a benzene ring with R_9 is -H or halo and R_{10}, R_{11} is -H or R_8 is 2-thienyl with R_{12} is -H.

3. The compound of claim 2 wherein R_5 is $-CH_3$.

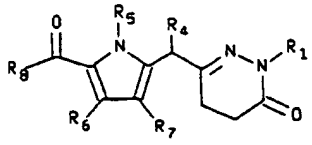
4. The compound of claim 3 wherein R_6 is $-CH_3$ and R_8 is a benzene ring with R_9 is -H or halo and R_{10}, R_{11} is -H..

5. The compound of claim 4 wherein R_9 is -Cl.

6. The compound of claim 4 wherein R_9 is -Br.

7. The compound of claim 3 wherein R_6 is $-CH_3$ and R_8 is 2-thienyl with R_{12} is -H.

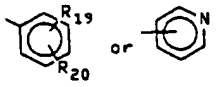
8. A compound having the structure:



wherein:

R_1 is -H, low r alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyloxy, substituted acyloxy, lower dialkylamino, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkene,

lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



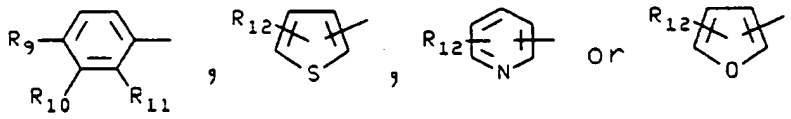
where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio; and

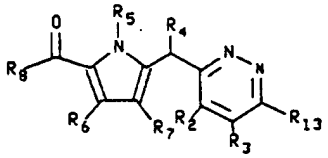
R_8 is:



where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; or pharmaceutically acceptable salts thereof.

9. The compound of Claim 8 wherein R_1 is -H; R_4 is -H; R_5 is $-CH_3$; R_6 is $-CH_3$; R_7 is -H; and R_8 is a benzene ring, where R_9 is -Cl; and R_{10} and R_{11} are -H.

10. A compound having the structure:



wherein:

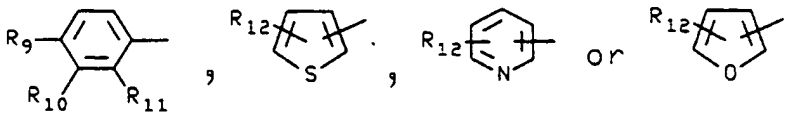
R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio;

R_8 is:

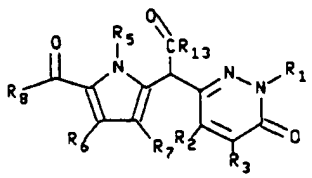


where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; and

R_{13} is lower alkoxy, mercapto, lower alkylthio, $-NR_{21}R_{22}$ or $-O-(CH_2)_m-NR_{21}R_{22}$; where m is an integer from 1 to 6, R_{21} is -H or lower alkyl and R_{22} is -H or lower alkyl, and where R_{21} and R_{22} may be taken together with N to form a ring of three to five carbon atoms which may include one member that is -O-, -S-, or $-N(R_{23})-$ where R_{23} is -H or lower alkyl; or pharmaceutically acceptable salts thereof.

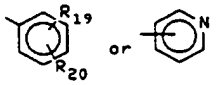
11. The compound of Claim 10 wherein R_2, R_3 and R_4 are -H; R_5 and R_6 are-CH_3; R_7 is -H; R_8 is a benzene ring, where R_9 is -Cl, and R_{10} and R_{11} are -H; and R_{13} is $-OCH_3$, $-OCH(CH_3)_2$, $-OCH_2CH_3$, $-O(CH_2)_2$-morpholino (HCl salt), $-NHNH_2$, $-NH_2$ or -SH.

12. A compound having the structure:



wherein:

R_1 is -H, lower alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyloxy, substituted acyloxy, lower dialkylamino, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkene, lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



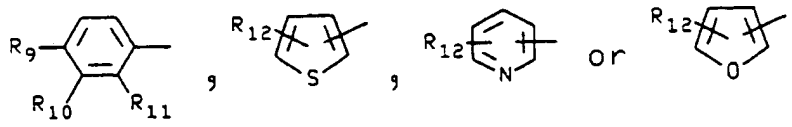
where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio;

R_8 is:



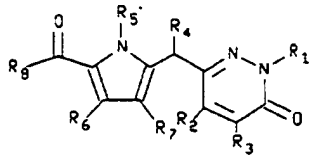
where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; and

R_{13} is lower alkoxy, mercapto, lower alkylthio, $-NR_{21}R_{22}$ or $-O-(CH_2)_m-NR_{21}R_{22}$; where m is an integer from 1 to 6, R_{21} is -H or lower alkyl and R_{22} is -H or lower alkyl, and where R_{21} and R_{22} may be taken together with N to form a ring of three to five carbon atoms which may include one member that is -O-, -S-, or $-N(R_{23})-$ where R_{23} is -H or lower alkyl; or pharmaceutically acceptable salts thereof.

13. The compound of Claim 12 wherein R_1, R_2 and R_3 are -H; R_5 and R_6 are $-CH_3$; R_7 is -H; R_8 is a benzene ring, where R_9 is -Cl and R_{10} and R_{11} are -H; and where R_{13} is -OH, -OH (Na salt), $-O(CH_2)_2$-morpholino (HCl salt) or $-OCH_3$.

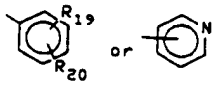
14. A pharmaceutical composition comprising (a) a therapeutically effective amount of a compound of any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof and (b) at least one pharmaceutically acceptable excipient.

15. A process for the preparation of a compound having the structure:



wherein:

R_1 is -H, lower alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyloxy, substituted acyloxy, lower dialkylamino, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkene, lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

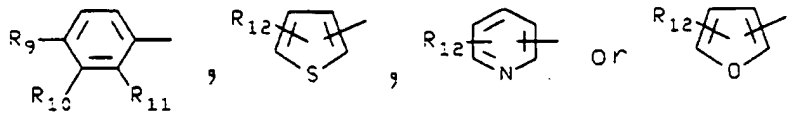
R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

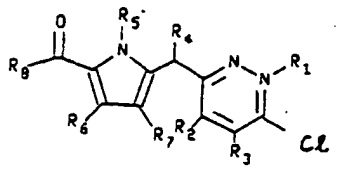
R_6 and R_7 are independently selected fr m the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio; and

R_8 is:



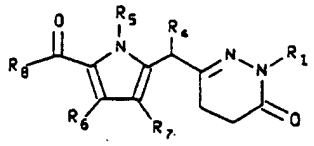
where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; or a pharmaceutically acceptable salts thereof, the process comprising:

(1) hydrolyzing a compound having the structure:



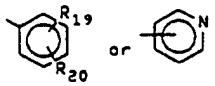
wherein R_1 is H and R_2 through R_{24} are as described above;
(2) optionally followed by reacting the thus-formed compound with a compound of the formula R_1X, wherein R_1 is other than H and X is a leaving group;
(3) optionally followed by the formation of a pharmaceutically acceptable salt.

16. A process for the preparation of a compound having the structure:



wherein:

R_1 is -H, lower alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyloxy, substituted acyloxy, lower dialkylamino, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkene, lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

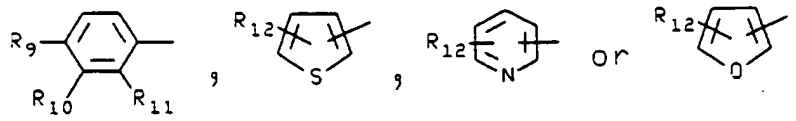
R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and

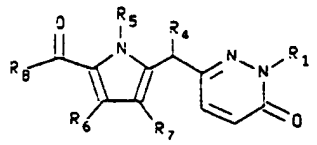
lower alkylthio; and

R_8 is:



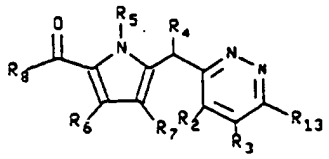
where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; or a pharmaceutically acceptable salts thereof, the process comprising:

reducing a compound having the structure:



wherein R_1 through R_{24} are as described above; optionally followed by the formation of a pharmaceutically acceptable salt.

17. A process for the preparation of a compound having the structure:



wherein:

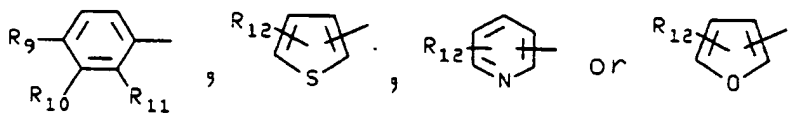
R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_4 is -H, lower alkyl or -CN;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio;

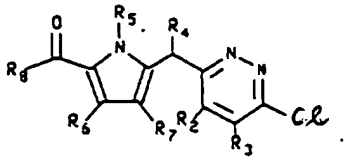
R_8 is:



where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; and

R_{13} is lower alkoxy, mercapto, lower alkylthio, $-NR_{21}R_{22}$ or $-O-(CH_2)_m-NR_{21}R_{22}$; where m is an integer from 1 to 6, R_{21} is -H or lower alkyl and R_{22} is -H or lower alkyl, and where R_{21} and R_{22} may be taken together with N to form a ring of three to five carbon atoms which may include one member that is -O-, -S-, or $-N(R_{23})-$ where R_{23} is -H or lower alkyl; or a pharmaceutically acceptable salts thereof, the process comprising:

reacting a compound having the structure:

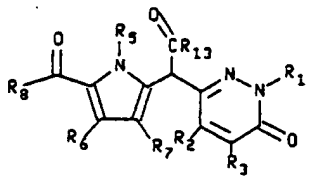


wherein R_2 through R_{23} are as described above;

with a compound of the formula $R_{13}H$ wherein R_{13} is as described above;

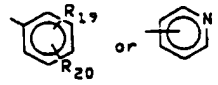
optionally followed by the formation of a pharmaceutically acceptable salt.

18. A process for the preparation of a compound having the structure:



wherein:

R_1 is -H, lower alkyl, halo-lower alkyl, acetyl, substituted acetyl, $-(CHR_{24})(CH_2)_nR_{14}$, $-(CHR_{24})(CH_2)_nC(O)R_{15}$, $-(CHR_{24})(CH_2)_nC(O)NR_{16}R_{17}$ or $-CHR_{24}R_{18}$; where n is an integer from 0-5, R_{14} is -CN, -OH, lower alkoxy, lower acyloxy, substituted acyloxy, lower dialkylamino, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkene, lower alkyne or methane sulfonamido; R_{15} is lower alkoxy; R_{16} and R_{17} are independently selected from the group consisting of -H and lower alkyl; R_{18} is:



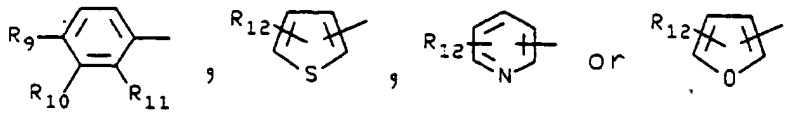
where R_{19} and R_{20} are independently selected from the group consisting of -CN, halo, lower alkoxy and lower alkyl; and R_{24} is -H, lower alkyl or phenyl;

R_2 and R_3 are independently selected from the group consisting of -H, halo and $-CH_3$;

R_5 is -H or lower alkyl;

R_6 and R_7 are independently selected from the group consisting of -H, halo, lower alkyl, lower alkoxy and lower alkylthio;

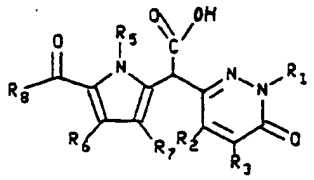
R_8 is:



where R_9 is -H, halo, lower alkyl, halo-lower alkyl, amino, lower dialkylamino, lower alkyl amido, lower alkylthio, lower alkoxy, lower alkene and lower alkyne; R_{10} and R_{11} are independently selected from the group consisting of -H, halo and $-CH_3$; and R_{12} is -H, -Cl or $-CH_3$; and

R_{13} is lower alkoxy, mercapto, lower alkylthio, $-NR_{21}R_{22}$ or $-O-(CH_2)_m-NR_{21}R_{22}$; where m is an integer from 1 to 6, R_{21} is -H or lower alkyl and R_{22} is -H or lower alkyl, and where R_{21} and R_{22} may be taken together with N to form a ring of three to five carbon atoms which may include one member that is -O-, -S-, or $-N(R_{23})-$ where R_{23} is -H or lower alkyl; or a pharmaceutically acceptable salts thereof, the process comprising:

reacting a compound having the structure:



wherein R_1 through R_{24} are as described above;

with a compound of the formula $R_{13}H$ wherein R_{13} is as described above;

optionally followed by the formation of a pharmaceutically acceptable salt.

19. A compound whenever prepared according to a process as claimed in any one of claims 15 to 18.

20. A compound as claimed in any one of claims 1 to 13 for use of a therapeutic agent, especially for the treatment of inflammation and/or pain.

21. Use of a compound as claimed in any of claims 1 to 13 as a therapeutic agent, especially for the treatment of inflammation and/or pain.

22. The invention as hereinbefore described.

23. A method of treating inflammation and pain comprising the step of administering to a mammal in need of said treatment a therapeutically effective amount of a compound as claimed in any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 95 11 8227

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	FR-A-2 316 942 (MCNEIL LABORATORIES INCORPORATED) * page 16; claims * ---	1,8,10, 12	C07D403/06 A61K31/50
A	FR-A-2 081 455 (MCNEIL LABORATORIES INCORPORATED) * claim 1; table I * ---	1,8,10, 12	
A	US-A-4 347 187 (MUCHOWSKI ET AL.) * claim 1 * ---	1,8,10, 12	
A,D	US-A-3 752 826 (J.R. CARSON) * claims * --- -/--	1,8,10, 12	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
BERLIN	27 March 1996	Frelon, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 95 11 8227

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CHEMICAL ABSTRACTS, vol. 98, no. 9, 28 February 1983 Columbus, Ohio, US; abstract no. 65202k, * abstract * & AGENTS ACTIONS, vol. 12, no. 5-6, 1982 pages 684-690, W.H. ROOKS II ET AL. ---	1,8,10, 12	
A	FR-A-2 375 234 (SYNTEX INC.) * page 1-12 * ---	1,8,10, 12	
A	CHEMICAL ABSTRACTS, vol. 106, no. 19, 11 May 1987 Columbus, Ohio, US; abstract no. 156207r, * abstract * & JOURNAL OF MEDICINAL CHEMISTRY, vol. 30, no. 5, 1987 WASHINGTON US, pages 820-823, J.M. MUCHOWSKI ET AL. ---	1,8,10, 12	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	CHEMICAL ABSTRACTS, vol. 100, no. 5, 30 January 1984 Columbus, Ohio, US; abstract no. 34432r, * abstract * & J. HETEROCYCL. CHEM., vol. 20, no. 4, 1983 pages 1027-1030, A.C. GOUDIE ET AL. ---	1,8,10, 12	
A	EP-A-0 068 460 (MERCK & CO., INC.) * abstract * --- -/--	1,8,10, 12	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 95 11 8227

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	WO-A-83 00863 (DIAMOND SHAMROCK CORPORATION) * abstract * ---	1,8,10, 12	
A	CHEMICAL ABSTRACTS, vol. 91, no. 7, 13 August 1979 Columbus, Ohio, US; abstract no. 56936f, * abstract * & EUR. J. MED. CHEM. - CHIM. THER., vol. 14, no. 1, 1979 pages 53-60, G. NANNINI ET AL. -----	1,8,10, 12	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

EPO FORM 1503 03.82 (P04C10)

EP 95 11 8227

-C-

Remark: Although claims 21-23 are directed to a method of treatment of (diagnostic method practised on) the human/animal body (Art. 52(4) EPC) the search has been carried out and based on the alleged effects of the compound/ composition